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THE INFLUENCE OF THE BLOOD PRESSURE IN UROGRAPHIC EXAMINATION[1]

(Preliminary Report)

by

Ingmar Wickbom

With the introduction of intravenous urography a radiological method was obtained by the aid of which it became possible not only to study the anatomy of the renal pelvis, as in retrograde pyelography, but also the physiology of the kidney. This possibility has been further extended by the use of abdominal aortography in combination with urography. Several factors have to be taken into account in such studies of the function of the kidney, perhaps one of major importance being the fluid balance of the patient at the moment of the investigation. But the importance of the blood pressure in this connection does not seem to have received particular attention in the literature. Some observations that the present author has made in examinations by urography alone, after intravenous injection of contrast, or in combination with abdominal aortography, have led him to the opinion that these questions call for a more detailed study.

Case I. A 75-year-old woman, having frequent attacks of cystitis. N-residue 35 mg.-%. At one time, the blood pressure prior to the examination amounted to 210/115 mm Hg. A conventional intravenous injection of 20 cc 35 % umbradil was made without appreciably affecting the patient. A picture was taken after 3 minutes, followed by a compression which was well endured. On a picture taken 28 minutes after the injection there was still no contrast to be observed in the renal pelves, but the kidneys had increased somewhat in density. The blood pressure was measured and proved to have fallen severely. In spite of that the patient was still almost unaffected. As the systolic pressure was only 70 mm Hg, 1 cc efedrin was given intravenously (35 minutes after the injection of the contrast). After another minute, the blood pressure had risen to 150 mm Hg. On a picture produced after a further 2 minutes, the renal pelves were well filled with contrast.

[1] From the Roentgen Department of the Serafimer Hospital, Stockholm, Sweden (Director: Prof. E. LINDGREN).

Submitted for publication April 1, 1950.

Fig. 1. Case I.
Picture taken 28 minutes after contrast injection. Still there is no contrast to be observed in the renal pelves. Blood pressure 70 mm. Hg. The kidneys are clearly visible due to contrast accumulation.

Fig. 2. Case I.
Pict. taken 35 minutes after contrast injection. Blood pressure 150 mm. Hg. The renal pelves are fairly well filled with contrast.

Case II. 70-year-old man with infection of the urinary tract. Conventional intravenous injection of 20 cc 35 % umbradil was made. After 3 minutes, some contrast secretion started on both sides which later increased somewhat. The compression, which was applied after that the 3 minute-picture had been taken, was to begin with well endured, but about 25 minutes after the injection the patient had a reaction, turned pale and perspiring. The compression was eased somewhat and as the blood pressure had fallen to 55 mm Hg, the patient was given 1 cc efedrin intravenously. The blood pressure rapidly rose to 95 mm. On a picture taken immediately before the compression was

Fig. 3. Case II.
Picture taken 18 minutes after contrast injection. A somewhat incomplete filling of the renal pelves is seen.

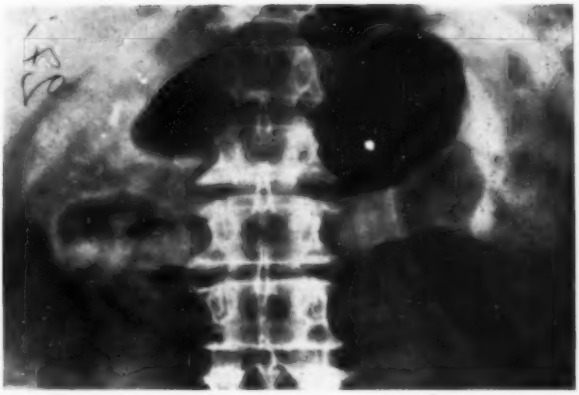

Fig. 4. Case II.
+ 7 minutes after contrast injection. Practically no contrast can be observed in the pelves. Blood pressure 55 mm. Hg.

released there was practically no contrast to be seen in the renal pelves, but 5 minutes later, when the blood pressure had risen to 95 mm, the pelves were well filled with contrast.

In both these cases, there was thus no contrast secretion as long as the blood pressure was low but it started as soon as the blood pressure had risen. There must consequently be a definite connection with the fall in blood pressure. It is well known from kidney physiology that urinary discharge ceases when the systolic blood pressure has fallen to about 70 mm Hg. At this level, the orthostatic pressure in the capillaries (two

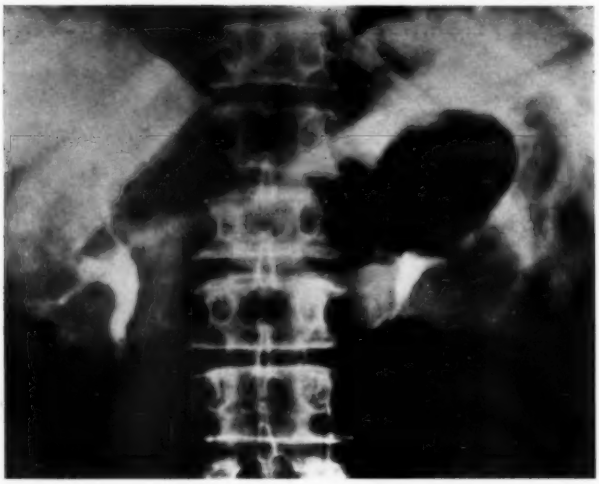

Fig. 5. Case II.
The renal pelves are again filled with contrast. Blood pressure 95 mm. Hg.

thirds of the arterial pressure, *i. e.* 45 mm Hg) will be approximately equal to the pressure in the renal pelves (normally about 5 mm Hg) added to the osmotic pressure due to the blood-albumin (about 40 mm. Hg). It is, however, more difficult to indicate any definite reason for the fall in blood pressure. In some cases where urography in combination with aortography was performed under anaesthesia (narcotal) the same phenomenon was observed, *i. e.* that contrast secretion was inhibited as long as the blood pressure was low despite the fact that the primary staining of the kidneys due to contrast filling of the capillaries was normal. It is possible that in those cases the fall in blood pressure was due to the anaesthesia, but it may also be suspected that the contrast medium could have played some part (experiments on animals have shown that 70 % diodrast may cause fall in blood pressure). As to the described cases, the fall in blood pressure would seem primarily to be due to the compression, especially of aorta and possibly through reflex in the sympathetic nervous system.

During urography, it does not infrequently happen that the contrast filling of the renal pelvis is imcomplete, although the compression of the ureters appears effective. The author has gained the impression that such incomplete filling seems to occur particularly in cases where the patient has difficulty in tolerating the compression, so that he has a reaction and, perhaps, turns pallid and perspiring. In many cases at least, this seems to be due to the fall in blood pressure.

The practical implications of the observations made would be that the blood pressure should be measured in such cases and that efedrin should be administered to raise the blood pressure if it is low. The author also intends to make an attempt at elucidating more fully the causes of the fall in blood pressure.

SUMMARY

If the blood pressure falls to about 70 mm. Hg the urinary discharge ceases and no contrast filling of the renal pelves is obtained in urography. Accordingly an unsatisfactory result in urography may be due to such a fall in the blood pressure. This is exemplified in 2 cases reported.

ZUSAMMENFASSUNG

Wenn der Blutdruck auf etwa 70 mm Hg sinkt, so hört die Harnabsonderung auf, und bei der Urographie erhält man keine Kontrastfüllung der Nierenbecken. Das unbefriedigende Ergebnis einer Urographie kann folglich durch solch ein Sinken des Blutdruckes bedingt sein. Dies wird durch 2 wiedergegebene Fälle veranschaulicht.

RÉSUMÉ

Quand la tension artérielle tombe à environ 70 mm. de mercure la sécrétion urinaire s'arrête et l'urographie ne donne plus d'image de contraste au niveau des bassinets. Par conséquent, la réponse insuffisante d'un examen urographique peut tenir à pareille chute de la pression du sang. Ce fait est illustré par la relation de deux cas.

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THE PRACTICAL ROENTGENOGRAPHIC IMPORTANCE OF RECIPROCITY LAW FAILURE[1]

by

Arne Frantzell

Precise roentgen film sensitometry is a laborious and time-consuming procedure involving the use of fairly complex apparatus and, in addition, requiring much experience on the part of the worker. In practice, therefore, the sensitivity of a new emulsion is often estimated by comparing it with another emulsion with known characteristics. Probably the most usual way of performing such comparisons is to place a sample of each film adjacently in the same casette and to make an exposure, so that half the object is depicted on each film sample. Both pictures are then developed simultaneously for equal periods in the same developer. The emulsion yielding the more gradated picture is held to be more sensitive.

That the more gradated and therefore denser film should be considered more sensitive may seem obvious, although nothing definite is known concerning the magnitude of the sensitometric difference. Nevertheless, the experiment may yield fallacious results if certain special considerations are not taken into due account. The first point is that the casette should be irradiated as uniformly as possible. Therefore the roentgen opacity and thickness of the object must be consistent in each half of the picture. Secondly, the films should not only be developed simultaneously for equal periods in the same developer, they must really be *fully developed:* there must be no risk that either of the films would have become denser had it remained longer in the developer. (To be fully developed different emulsions sometimes require different lengths of time.) Thirdly, a high fog level must not be confused with superior photochemical sensitivity of the emulsion.

[1] Submitted for publication, March 30, 1950.

Unexpected Results of Comparative Sensitivity Tests

Even if the above conditions are satisfied, however, such tests may only yield highly approximate results, but results that sometimes are downright misleading. This will now be exemplified.

Fig. 1 is a roentgenograph of the lungs taken in *one* exposure, the right thorax half being exposed on Gevaert film (emulsion no. 17257) and the left on Ilford film (emulsion no. 947). The films were exposed side by side between intensifying calcium tungstate screens (Patterson), both films were developed simultaneously for 5 minutes in »Gevaert 230» developer, which had been found fully to develop both film brands in about 4 minutes; the negatives were printed simultaneously on paper of the same quality. Both the negatives and the prints showed that the left thorax half (Ilford film) was denser and much more gradated than the right.

Fig. 2 is a roentgenograph of a pelvis taken similarly to fig. 1, *i. e.* the right half on Gevaert film and the left on Ilford film. The films came from the same packages as in the above experiment; the same casettes and screens were used; the mode of developing and printing was the same. In this case the left picture half was not better than of the right, if anything, at least in parts, the right picture was rather better.

Discussion of the Unexpected Results

If the above results were to be used to estimate the relative sensitivities of the two film brands, the first experiment would incontrovertibly indicate that the Ilford film was more sensitive; the second would suggest that the Gevaert film was equivalent if not slightly superior. This most remarkable discrepancy may naturally give rise to various speculations, particularly as regards the uniformity of the experiments and their absolute comparableness. However, several repetitions of the experiments yielded parallel results, *i. e.* Ilford film was superior for lung roentgenographs and Gevaert film for pelvis roentgenographs.

In order to elucidate the cause or causes of this effect, which at first sight may appear not to be susceptible of a simple explanation, it is of course first necessary to discover whether there were any differences in principle between the two experiments, *i. e.* between the lung exposure and the pelvis exposure. The differences are set forth in the below table, from which it among others will be seen that the lung picture was exposured one hundred time as long as the pelvis picture.

Object	Roentgen equipment used	Focal Dist.	KV P	mA-sec.	mA	Exposure in secs.
Lungs	6-rectifyer machine	150 cm	60	12	300	0.04
Pelvis	4-rectifyer machine	80 cm	64	240	60	4.0

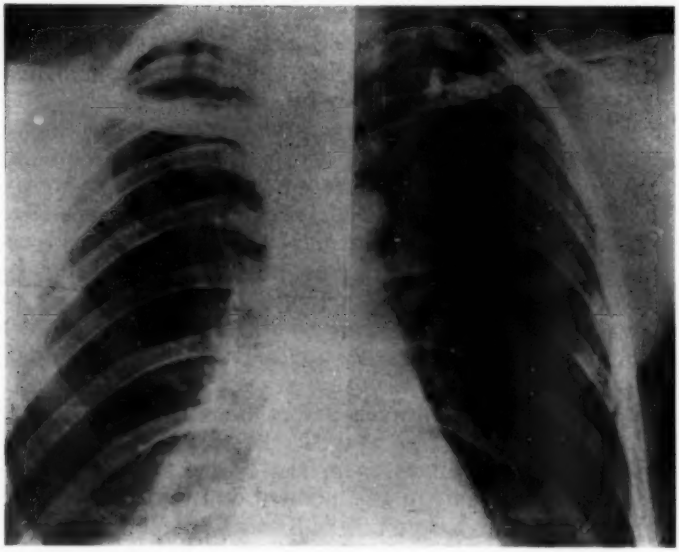

Fig. 1.

Gevaert 0.01 Secs. Ilford

Fig. 2.

Gevaert 4.0 Secs. Ilford

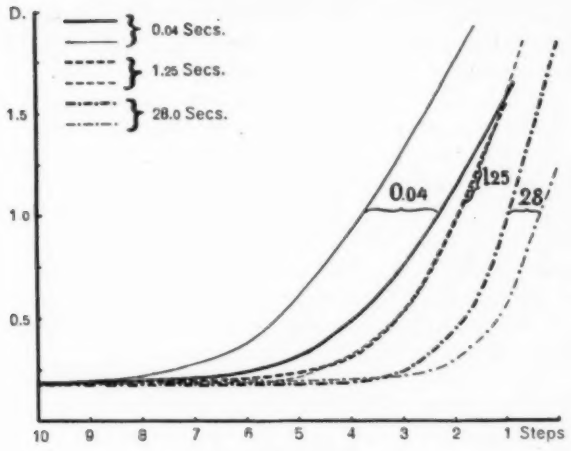

Fig. 3.

Intensifying Screens
Bold lines = Gevaert. Light lines = Ilford.

Sensitometric Tests Using a Copper Step-Wedge and Intensifying Screens

Since it could be assumed on good grounds that the discrepant results were due to the large difference in exposure time, a new experiment, eliminating variations in equipment, kilovoltage and milliamperage, was devised along the same lines as the old. Moreover, the body-part object was replaced with a copper stepwedge, thus guaranteeing equal roentgen transmission to both film samples. The new experiment was carried out as follows:

The casette with the two film samples (the same emulsion as before) and the step-wedge superimposed on it was placed 35 cm below the focus of the roentgen tube used to photograph the pelvis. The first exposure was made in 0.04 secs. at 30 mA and 60 kV. In order to find the effect of a longer exposure, the focal distance for the next picture was increased to 196 cm and the exposure time, according to the law of inverse squares, to 1.25 secs. A third exposure was made with the focal distance 925 cm and the exposure time 28 secs. The kilo voltage and milliamperage were kept constant throughout. After simultaneous development, all the films were photometered and the results plotted in a graph. The film densities were entered along the ordinate of an ordinary system of coordinates, and the numerical thickness of the corresponding steps along the abscissa. See fig. 3. It will be seen from the curves that the sensitivity of the Ilford film is decidedly superior to that of the Gevaert film for an exposure time of 0.04 secs. The films

become approximately equivalent when the exposure time is increased to 1.25 secs., and when the exposure time is further increased to 28 secs. the Ilford film is decidedly inferior to the Gevaert film. Thus, the same effect made itself felt in the latter experiments as in the tests with lung and pelvis exposures described above. Furthermore, the curves also demonstrate that longer exposure times are associated with a gradational change towards an increasing gamma, *i. e.* a higher degree of contrast. In this paper I shall not elaborate the reasons for the latter effect, but I shall make a few statements concerning its practical consequences. At least in part the apparent loss of sensitivity for both films as the exposure time increases may be an imaginary, for the longer focal distances must entail increased atmospheric absorption of the roentgen radiation. The varying differences in sensitivity, on the other hand, cannot be so explained; they must be attributed to quite different causes.

Schwarzschild's Principle

So far as I have been able to find, the photographic effect described in the foregoing must be attributed to reciprocity law failure in the form of a so called Schwarzschild effect which is more noticeable in the Ilford emulsion than in the Gevaert emulsion.

The reciprocity law was formulated by BUNSEN & ROSCOE in 1876. The law states that the effective action of light is constant when the product of the intensity by the time of action is constant. Accordingly, the light intensity and the exposure time are reciprocals. (In roentgenography, the figure for the milliamperage may, as we know, substitute for the figure for light intensity, since these two units are directly proportional.) However, some later authors, particularly German astronomers, have pointed out that this law is not always valid. The very minute light intensities, which often must be registered by astronomers, obviously require extremely long times of exposure, but it is a fact that they as a rule must be lengthened considerably over and above the figure arrived at according to the reciprocity law. In 1899 SCHWARZSCHILD formulated a law stating that the photochemical effect should not be assumed equal to I by t (light intensity multiplied by exposure time), but to I by t^p, where p usually is less than unity. This law is as a rule termed Schwarzschild's law, and the exponent p is often called Schwarzschild's exponent. SCHWARZSCHILD was the first to discover that p varies from emulsion to emulsion, and it has later been proved that the factor in question is not even constant for the same emulsion but varies in different ranges of light intensity.

The cause of the Schwarzschild effect was not understood until recent times. It has been shown that all cases of reciprocity law failure

are due to the fact that a latent photographic image cannot be produced in the light-sensitive emulsion unless several quanta of light are absorbed by silver halide crystals suspended therein. In other words, to become developable the crystals must absorb a fair number of light quanta. If the absorption of the required quanta is spread over a relatively long time, *i. e.* if the exposure time is relatively long, it may occur that the action of some absorbed quanta will already have receded before the silver halide grain has absorbed a sufficient number to become developable. Consequently, the Schwarzschild effect is equivalent to a kind of instability of the grain while the latent image is being formed, which instability will have a greater effect as the exposure time increases. These latter considerations apply to radiation with a relatively low content of energy, *i. e.* with a low frequency. In exposures with visible light, the number of absorbed quanta necessary to render the silver halide crystal developable ranges from a few hundreds up to about one thousand. It is known that the light mainly is absorbed within the halide ions of the crystal and that each quantum splits off one electron from the ion that absorbs it. When photography takes place with high-energy radiation, direct roentgenography for example, a single radiation quantum is most often enough to cause the ionization effects in the crystal which make it developable, the reason being that each quantum of such high-energy radiation perhaps splits off one thousand electrons from the same number of halide ions. Consequently, direct roentgenography involves no reciprocity law failure. The Schwarzschild exponent is unity.

Sensitometric Tests Using a Copper Step-Wedge and no Intensifying Screens

This latter fact offers some means of checking further, whether in the experiments described above it actually was a Schwarzschild effect that caused the films to show varying sensitivity differences for different exposure times: the sensitivity differences should not manifest themselves in a repetition of the last experiment without the intensifier screens, *i. e.* an arrangement such that the copper step-wedge is photographed direct with roentgen radiation. Simultaneously a measure would be obtained of the influence of atmospheric absorption at the various focal distances. Fig. 4 illustrates photometric curves of such an experiment, the focal distances being the same as in the first two parts of the former experiment, viz. respectively 35 and 196 cm. Obviously the exposure times had to be increased owing to the absent intensifying factor. The exposure time at 35 cm was 0.5 secs. and at 196 cm 15.6 secs. A third, longer distance could not be tried in this case as the exposure

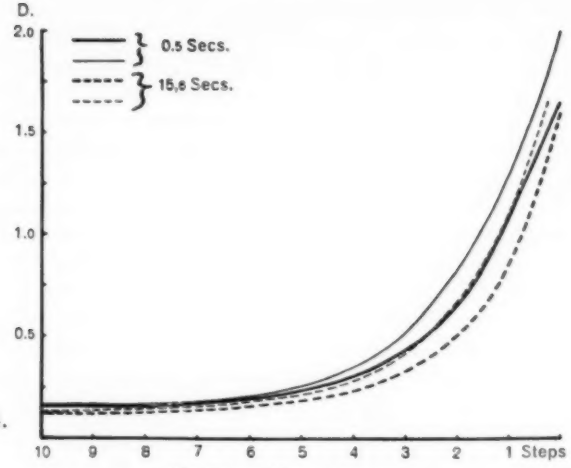

Fig. 4.

No Intensifying Screens
Bold lines = Gevaert. Light lines = Ilford.

time then would have become excessive. The curves in fig. 4 show that this time the sensitivity differences between the experiments did not vary with the exposure times. Both films exhibited lessened sensitivity with increasing distances, but this time it for the most part apparently was non-factual and wholly due to the increased atmospheric absorption at greater focal distances.

Practical Consequences of the Observed Effects

With this paper the author has in the first place intended to point out the practical roentgenographic consequences of reciprocity law failure, and in the second place to emphasize the importance of the same phenomena in more precise roentgen film sensitometry. In this connection it ought perhaps to be stated that *the intention has not been to single out the brand of film having the best properties*, and which therefore would be preferable for the purposes of roentgenographic diagnosis. The reason why Gevaert and Ilford film were selected for mutual comparison is that when the experiments were performed the commercially obtainable Gevaert and Ilford emulsions proved to be most different as regards the Schwarzschild effect and therefore illustrated it to most advantage. Since the Schwarzschild effect seems able to vary from emulsion to emulsion, it is by no means certain that the sensitivity differences at different exposure times which are discussed in this paper will be characteristic

also of coming emulsions of these film brands. Thus, a new experiment performed about 6 months later than the above experiment and with new emulsions admittedly yielded a plainly measurable discrepancy in the above direction, but the sensitivity differences for different exposure times were much smaller on this occasion so that they manifested themselves only in highly accurate experiments with the copper step-wedge. For these reasons among others, the author has refrained from attempting to measure the Schwarzschild effect's degree in the tested emulsions, it being very little profitable to know this quantity for an emulsion that, when this is published, no longer is in the market and has been replaced by other emulsions having in part other properties.

In the opinion of the author, the practical conclusions that should be drawn from the observations reported in this paper are as follows:

If the relative sensitivity of two roentgen film emulsions is estimated in the manner described in the opening paragraphs of this paper, it should be understood that *the result obtained is conclusive only for the time of exposure used in the experiment.* Thus, for example, if the lungs are exposed on two different emulsions lying side by side in the same casette and the sensitivity of one of the films far surpasses that of the other, it may be likely that the same will be the case when a pelvis is photographed, but this is not necessary. The experiment ought therefore to be performed with at least two different times of exposure if the applicability of the film in the ordinary range of roentgenographic diagnosis is being studied; for example, one exposure of some hundreths of a second and one of some whole seconds.

From the experiments made, the conclusion may also be drawn that films may exist which are particularly suited for examinations such as usually are performed with short exposure times, just as there may be other kinds if films which are more adapted for examinations requiring long exposures.

If roentgen film is to be employed for other purposes than medical roentgenographic diagnosis, its sensitivity must be tested separately at the exposure times which then may be used. What the author has in mind is that roentgen film now and then has been employed in high-voltage research, at the Institute of High Tension research at the University of Upsala (Chief: Professor Harald Norinder). In such cases the exposure times are extremely short, sometimes as short as some microseconds. The most suitable film for such ultrashort exposures cannot be selected by means of experiments within the standard range of exposure times. It should be noted that it by no means is certain that an emulsion which is more sensitive at 1/100 sec. than at 1 sec. also is more sensitive at ultrashort exposure times. As regards the emulsions discussed in this paper, the author has compared the sensitivity of the emulsions

Fig. 5.

Bold line = Gevaert. Light line = Ilford.

at an exposure time of 1/10,000 sec., the exposure being made with the aid of a discharge flash lamp. It turned out that the Ilford film was more sensitive than the Gevaert film, but that the difference was not as large as at 0.04 secs. The roentgen film sensitometry may become of even greater importance in roentgenography since condensor-type machine, using ultrashort exposure times, are likely to become increasingly popular.

Naturally, the deviations from the reciprocity law are most important in the sphere of precise roentgen film sensitometry. In this paper I shall not deal in detail with the methods of avoiding mistakes due to the Schwarzschild effect in roentgen sensitometry, as I aim to discuss these matters more closely in a forthcoming paper. Here it will suffice to point out that, judging by literature, the Schwarzschild effect plays but a minor rôle in roentgen film sensitometry. Fig. 5, however, shows an example of how wrongly the properties of an emulsion may be evaluated by basing a characteristic curve on a logarithmic time scale with a minimum time of 10 secs. Fig. 5 shows that the Ilford emulsion which actually has a higher sensitivity at 0.04 secs. than the Gevaert film it is being related to, if the above logarithmic method is used not only appears to be much less sensitive than the Gevaert film but seems to have inferior contrastive properties, *i. e.* a lower gamma, than the Gevaert emulsion. The latter factor, moreover, is an additional expression of the increasing influence of the Schwarzschild effect as the exposure times increase.

In conclusion, the author should like to report another observation made in the course of the experimental work described in this paper.

Considering the curves in fig. 3, we observe that not merely the sensitivity but also the gradation has altered along with the time of exposure. This holds for both emulsions and implies *an increasing gamma as the exposure time increases*. Here and there in roentgenologic literature there are statements to the effect that better roentgenographs would be obtained by using lower milliamperage. This is quite surprising as the milliamperage does not influence the quality of the roentgen radiation, the latter only being affected by the kilovoltage. Observing this plain contrastive increase, however, one may ask if it might not be this effect that has been observed by some authors who wrongly have attributed it to amperage variations instead of to variations in the exposure time. Nevertheless, it is certain that superior contrast is obtained at long exposures because of gradational changes in the emulsion.

SUMMARY

A common method in practical roentgenography of comparing the sensitivities of two emulsions is to expose simultaneously two films placed adjacently in the same casette. The author demonstrates that the difference in sensitivity obtained thereby does not with certainty apply for other times of exposure than those used in performing the experiment. This observation is attributed to the possibility that the films may have different Schwarzschild effect. The practical roentgenographic importance of reciprocity law failure is discussed. It is also shown that the gradation of roentgen films changes as the exposure time increases, the contrast being much higher for long exposures than for short.

ZUSAMMENFASSUNG

Eine in der praktischen Röntgenologie gebräuchliche Method, die Empfindlichkeit von zwei Emulsionen zu vergleichen, besteht im gleichzeitigen Exponieren von zwei nebeneinander in ein und derselben Kasette angebrachten Filmen. Verf. zeigt, dass der hierbei erhaltene Empfindlichkeitsunterschied nicht notwendigerweise für andere Exponierungszeiten gilt als die im Experiment verwendeten. Diese Beobachtung wird auf die Möglichkeit zurückgeführt, dass die Filme verschiedenen Schwarzschild-Effekt haben können. Die praktische röntgenologische Bedeutung einer mangelnden Übereinstimmung wird besprochen. Ferner wird gezeigt, dass die Gradierung des Röntgenfilms mit zunehmender Exponierungszeit wechselt, indem der Kontrast bei langer Exponierung viel stärker ist als bei kurzdauernder.

RÉSUMÉ

Une méthode couramment employée en pratique radiographique pour comparer la sensibilité de deux émulsions consiste à exposer simultanément deux films placés côte à côte dans un même châssis. L'auteur démontre que la différence de sensibilité ainsi déterminée n'existe pas de façon certaine avec d'autres temps de pose que ceux qui furent utilisés pour l'expérience. Cette observation s'expliquerait par la possibilité que les films aient des »effets Schwarzschild» différents. L'auteur discute de l'importance, pour la pratique radiographique, de la carence de la loi de réciprocité. Il montre aussi

que la gradation des films Roentgen change avec l'augmentation du temps de pose, les contrastes étant beaucoup plus grands avec des expositions longues qu' avec des expositions courtes.

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FROM THE ROENTGEN-DIAGNOSTIC DEPARTMENT OF THE UNIVERSITY CLINICS OF LUND, SWEDEN (HEAD: PROFESSOR OLLE OLSSON)

FIBRO-OSTEOMA IN THE MANDIBLE OF A CHILD[1]

by

Anders Sonesson

The fibro-osteoma is an osteogenic, ossifying tumour, usually occurring in the bone of the cranium and most frequently in the jaws. It is said to show a predilection for young individuals. BILLING & RINGERTZ (1946) state that the frequency of the tumour is highest in the years around puberty. THOMA (1938 & 1945) is of the opinion that the fibro-osteoma usually occurs in the second and third decades of life. FUREDI (1935) reports 14 maxillary fibro-osteomas in patients 25—64 years of age and SCHLUMBERGER (1946) 12 cases (7 maxillary and 5 mandibular) in 10—37 year old patients. In BILLING & RINGERTZ' series the age limits were 10 and 57 years, but they say that in the youngest of the series the tumour probably began to develop when the patient was no more than 18 months old. In the oldest patient, who had a multiple tumour, the growth had been stationary for at least 15 years.

It has sometimes been doubted whether the growth is a tumour in the general concept of the word. It has even been suggested that the condition might be due to some kind of inflammation. BILLING & RINGERTZ consider it probable that the fibro-osteoma is not a true neoplasm, but a growing malformation. This opinion is not shared by FUREDI (1935), PHEMISTER & GRIMSON (1937) and THOMA (1938 & 1945). The disease is generally thought to be a slowly growing benign tumour.

In the course of its development from the very immature stage to the mature stage the tumour undergoes a usually patchy ossification. These patches may show very different stages of ossification in different parts of the lesion. Owing to the irregularity of this gradual ossification the tumour is able to present a histologically and roentgenologically varying picture with both mature and immature areas in one and the same growth.

The case to be reported and mentioned earlier by the author (SONES-

[1] Submitted for publication, May 26, 1950.

SON, 1950) differs from others of its kind in two respects: the age of the patient, who was only 2 years old when the neoplasm was first observed, and secondly, the rate of growth of the tumour, which was very rapid like that of a malignant process. The tumour was, of course, in the very immature stage.

Case history. L. K. H. N. Age 2 $^1/_2$ years. Surg. Clinic, Lund. 1810/48. In Oct. 1947 the patient was admitted to a district hospital on account of a tumour, which the parents had noticed hardly one month before. Examination on admittance: Normally developed child in good general condition. Temp: 37.2° C. Examination of heart, chest and abdomen revealed nothing pathologic.

Part of the mandible just before the angle was expanded by a smooth-surfaced, firm, but not tender, walnut-sized tumour bulging into half of the floor of the mouth. Submandibularly there was a pea-sized, not tender, rather soft lymph node.

Roentgen examination: »Signs of a large follicular cyst in right mandible. It is about 4 cm. in diameter and has destroyed the major part of the mandibular body and the entire alveolar process behind the first molar. It seems to have derived from the second molar, the crown of which is located in the bottom of the cyst.» (Fig. 1.)

The tumour was enucleated and in the bottom of the tumour cavity was a loose dental crown that was also removed.

On histologic examination of the enucleated tumour mass the pathologist suspected an osteogenic (osteoid) sarcoma, the degree of malignancy of which he could not determine.

Re-examination of the histological preparations revealed that an ossifying fibroma ought to be taken into consideration, which on account of the patient's age was unusually rich in cells.

In April, 1948, the patient was re-examined roentgenologically. The growth had in the meantime begun to give her more trouble. A large recurrence was observed and, judging by the roentgen picture, the extent of the lesion in the jaw had markedly increased. The patient was therefore referred to the Radiological Clinic, Lund. Her general condition was still good. On palpation it was observed that the region from the malar bone down to the angular portion of the mandible and to the middle of the floor of the mouth was involved by a large tumour. On intra-oral palpation through the small interspace between the upper jaw and the lower jaw a firm infiltration was felt in the mandible. From the angle to the mental portion of the mandible no jawbone but only a firm tumour could be palpated. No lymph nodes could be felt in the neck, in the supra- and infraclavicular regions, nor in the armpits.

Roentgen examination. »The right half of the mandible is expanded considerably by the tumour. There is a large, polycyclic destructive process. From the cuspid to the mandibular notch only a narrow strip of the base of the mandible is unchanged. The coronoid process is destroyed. Thin trabeculae extend from the surviving bone into the soft mass of the tumour. Since Oct. 1947 the lesion has increased considerably to a fair extent posteriorly but above all anteriorly, where the premolars have been lifted up and now lie in the periphery of the tumour. It cannot be decided definitely whether the tumour is an adamantinoma or a fibroma.

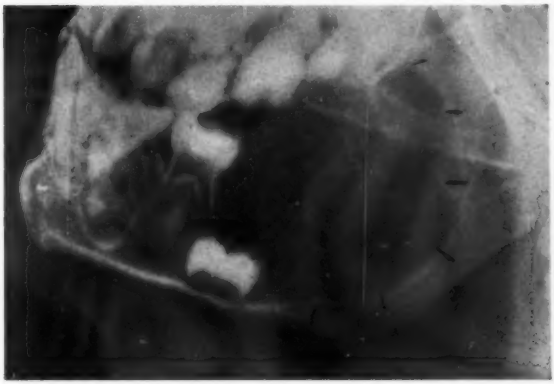

Fig. 1. Lateral view of mandible in Oct. 1947.

Roentgenography of the chest shows nothing pathologic (NORMAN)».

Irradiation was thought to be contra-indicated on account of the undesired effect it would probably have on the later growth of the jaw of such a small child. The child was therefore referred to the surgical department.

In order to find out whether the growth was malignant or not, angiography — in which the contrast medium was injected into the operatively exposed external carotid artery — was performed under intratracheal anesthesia. It showed that the arterial branches at the site of the tumour were displaced and distended. The blood supply to the tumour was rich. Neither pathologic vessels nor arterio-venous fistulae were observed (OLLE OLSSON). See Fig. 2.

At operation (STRÖMBECK) the right half of the mandible with the large tumour was resected medial to the right cuspid and ex-articulated.

Microscopy (of tumour in the resected specimen). »The mandibular tumour consists of osteoid trabeculae, which build a plexiform network displaying several areas of calcification. The trabeculae are embedded in connective tissue rich in cells, and many of them are lined with osteoblasts. A few scattered giant cells similar in type to those seen in epulides have formed. In its middle the tumour shows signs of necrosis and a tendency to cystic degeneration. The outer surface of the growth is well outlined by a fibrous capsule that has not been invaded. No mitoses are to be seen. The picture presents the characteristics of an osteo-fibroma. There are no difinite signs of malignancy. The extirpated submaxillary gland shows nothing remarkable. No signs of metastases were seen in the lymph nodes examined» (C. G. AHLSTRÖM).

The operation wound healed primarily and after three months there were no signs of recurrence.

The defect was later successfully filled with a bone graft.

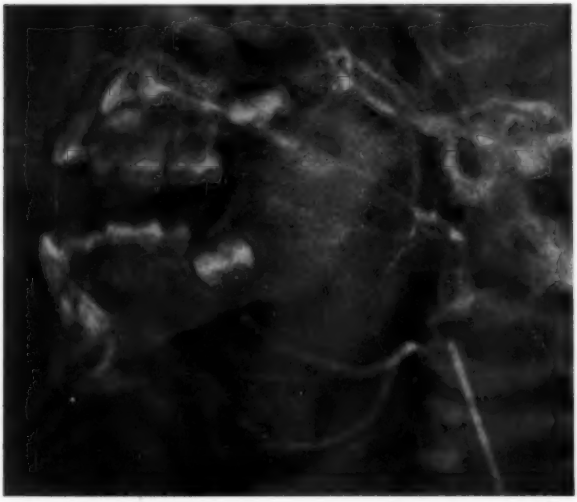

Fig. 2. Angiogram of the same mandible in May 1948.

Discussion

In the present case the patient was very young. In BILLING-RINGERTZ' case Nr. 22, which was the only case that could be traced in the literature available, the maxillary tumour was believed possibly to have begun at an even earlier age, but the clinical course was altogether different from that of the present case. In their case the tumour was located in the upper jaw and grew very slowly. Curettage was performed. There was a recurrence for which surgical intervention was not indicated until 3 years later (also this time curettage). Five years later, when the tumour again began to grow, partial maxillary resection was performed. A fibro-osteoma was discovered also in the lower jaw. The latter was of a fairly immature type. It was interesting to note that this girl, who was then 10 years old and whose hospital records I saw at Radiumhemmet, had menstruatio praecox (cf. Albright's disease with skeletal changes, liable to occur in females in association with pubertas praecox). No such disturbances had been observed in the early age of the patient in question and, at least so far, the tumour in this case has been solitary.

In contrast to earlier cases from the literature, the tumour under discussion had grown very rapidly and it presented a clear-cut clinical picture of a tumour. BILLING-RINGERTZ' opinion that the fibro-osteoma should probably be classed as a malformation is therefore not generally valid.

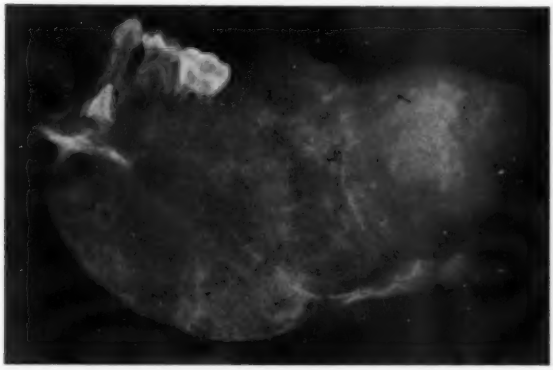

Fig. 3. Roentgenogram of the resected tumour in somewhat reduced scale.

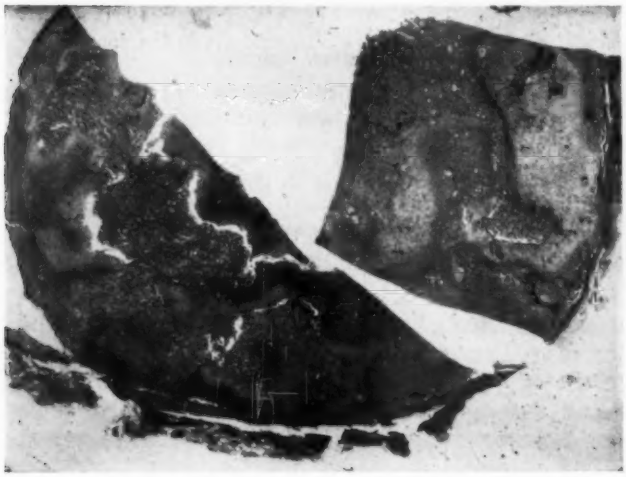

Fig. 4. Photomicrograph of a portion of the resected fibro-osteoma. Magnification: × 4.

The present case offers much of interest from a roentgenological point of view. It was admittedly diagnosed primarily as a follicular cyst, probably on account of the finding of a malposed tooth germ in the bottom of the lesion, but this diagnosis does not seem to be well founded. The distal root of the deciduous molar (not of the first permanent molar as was primarily assumed) was denudated by the tumour and, secondly, the

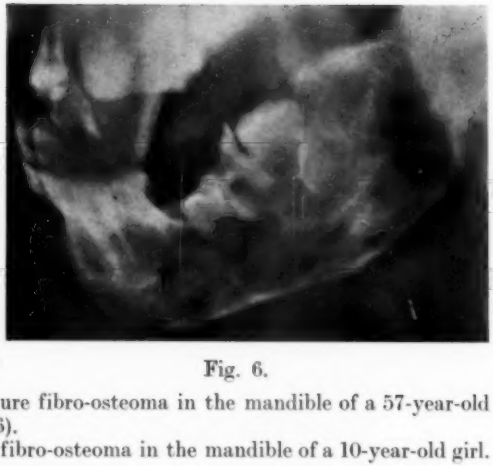

Fig. 5. Fig. 6.

Fig. 5. Tangential view of an immature fibro-osteoma in the mandible of a 57-year-old man. (Billing-Ringertz' case 6).

Fig. 6. Lateral view of an immature fibro-osteoma in the mandible of a 10-year-old girl. (Billing-Ringertz' case 22).

lesion was more opaque than an odontogenic cyst of a similar size would have been. A certain radiopaque indistinct design was recognizable in the tumour. Therefore close examination of the primary roentgenogram permitted the diagnosis of a tumour, although it was impossible at this stage roentgenologically to say anything as to its kind. The essentially distinct outline suggested a benign lesion. Later roentgenography suggested a central fibroma (fibromyxoma), which sometimes ossifies and often shows the small-lobulated polycyclic border of the type presented by the tumour in question. Angiography, which was in this case probably performed for the first time for diagnosing tumours of the jaws, also suggested a benign tumour.

Roentgenography of the resected specimen presented a picture of certain interest. A subtle but nevertheless visible polygonal pattern of characteristic appearance is to be seen in several areas in the roentgenogram. Annular densifications are to be seen in the tumour. Unfortunately the cliché was unable to bring out this pattern distinctly (Fig. 3). It is certainly due to the superimposition of polygonal trabeculae of osteoid tissue with commencing calcification. Fig. 4 which is a photomicrograph (low magnification) of the histological preparation of the tumour illustrates to a certain degree the delicate topographical formation of the osteoid trabeculae.

Whirl-like and garland-like structures and orange peel appearance seen in a certain type of mature fibro-osteomas have been described before, but not this polygonal net-like variant of the pattern in a very immature stage of the kind of tumour in question. This design may probably later be replaced by the above mentioned structures. BILLING & RINGERTZ write that in the very immature type, to which the present case undoubtedly belongs, the calcified structures may be so small, that they do not come out on the roentgen picture. In my opinion, however, if no-screen films are used and if the picture is taken under technically favourable conditions, the roentgenogram ought to be able to bring out such a pattern.

Such a design is probably no isolated feature of the fibro-osteoma. In a few of BILLING & RINGERTZ' cases (Nr. 6 and 22 in their paper) the roentgenograms of which were placed at my disposal by the courtesy of the chief of Radiumhemmet, Prof. ELIS BERVEN, similar structures could be detected. In a tangential picture of the mandibular tumour in their case Nr. 6 (see Fig. 5 above) it appeared in pea-sized meshes and in their case Nr. 22 the mandibular tumour (see Fig. 6 above) — especially in the anterior half — a similar arrangement could be seen, although with larger meshes in the coarse, blurred net. Here, too, the more central parts of the meshes contained small calcified areas, which might to a certain extent have blurred the picture, but a definite acinous structure is obvious in the original films. A recurrence in my material (SONESSON 1950, Fig. 103) showed a somewhat similar picture.

Fig. 4 shows that the tumour is divided also in rather large, somewhat angular lobes by fairly straight septa but it cannot be said whether this is characteristic of this kind of tumour or not.

SUMMARY

A description is given of a rapidly growing fibro-osteoma in the mandible of an only 2-year-old girl. The lesion must be definitely classified as a tumour.

ZUSAMMENFASSUNG

Beschreibung eines Falles von rasch wachsendem Osteofibrom des Unterkiefers bei einem 2jährigen Mädchen. Diese Veränderung ist definitiv als Tumor anzusehen.

RÉSUMÉ

Description d'un cas d'ostéofibrome, à croissance rapide, au niveau du maxillaire inférieur d'une fillette de deux ans. Cette lésion doit être classée sans conteste parmi les tumeurs.

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FROM THE ROENTGEN-DIAGNOSTIC DEPT., STATE DENTAL SCHOOL, MALMÖ, SWEDEN
(TEMP. HEAD: ANDERS SONESSON)

INTRA-OSSEOUS MUCUS-SECRETING AND CYSTIC EPIDERMOID CARCINOMA OF THE JAW[1]

by

Anders Sonesson

Cases of mucus-secreting and cystic epidermoid carcinomas have certainly been described in past years, but not intra-osseous ones. The tumour has recently been definitely differentiated as a special form of cancer. Pathogenetically it comes close to tumours of the mucous and salivary glands and occurs in regions containing such glands. In a series of 700 tumours of the major and minor salivary glands STEWART, FOOTE & BECKER (1945) found that about 5 per cent were »muco-epidermoid tumors». BERNIER (1946) observed an approximately equal frequency of this form of cancer among 38 mixed tumours of the lips — mainly of the upper lip. In an earlier paper of that year he reported some cases from a histogenic point of view and came to the conclusion that this kind of tumour is capable of appearing in three different forms, namely, as metaplasia of the epithelium in the duct of a mucous or salivary gland, as a benign epidermoid tumour, and as a malignant epidermoid tumour. The value of such a classification is doubted by inter alia LINELL, who 1948 described 12 cases. These tumours are generally thought to originate from the epithelium of the ducts of the mucous and salivary glands. Readers interested in further details of the histopathology and in literature on this type of cancer are referred to LINELL's paper. Illustrations of its histology are given in STEWART, FOOTE & BECKER's publication of 1945.

Like ordinary tumours of the mucous and salivary glands, the tumour in question is capable of proliferating into adjoining bone and there give rise to cyst-like lesions, but, judging by a perusal of the literature, only two cases with such changes in the jaw bones have hitherto been reported. They were described by BOSSART (1945), but he conceived them as variants

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of the adamantinoma and called them hypernephroid adamantinomas. He observed the micro-cystic structure of the tumour and the large clear cells in the epithelial lining of the small cysts. In his opinion these cells resembled those seen in hypernephroma. He thought the tumours to be epitheliomas of adamantinoma type originating from the oral mucosa. Hence, he did not recognize the true nature of the large mucus-secreting goblet cells.

The roentgen picture in BOSSART's first case is described as a multilocular, cyst-like lesion, located in the angular portion of the mandible and extending from the region of the wisdom tooth up to the base of the coronoid process. He states that the changes resemble those seen in an adamantinoma. In his second case the tumour was located in the posterior part of the alveolar process of the maxilla. This case presented no essentially characteristic roentgen picture and was assumed roentgenologically as chondroma or chondrosarcoma. The primary histological diagnosis was cancer, but on re-examination of the resected specimen (in this case the upper jaw was resected) BOSSART was able to demonstrate exactly the same kind of tumour as in the first case. In the maxillary case he was able to recognize the site of origin of the tumour in a small funnel-shaped pocket in the mucosa of the palatinal aspect of the alveolar process.

When collecting material for studying odontogenic cystic tumours of the jaws I observed three cases of mucus-secreting and cystic epidermoid carcinoma involving the bone of the lower jaw. As such cases have hitherto not been reported under their correct designation, a description seems to be justified.

Roentgenologically two of the cases were primarily assumed to be adamantinomas, and one was also diagnosed as such at the first routine histological examination.

Case 1. E. N. ♀ 63 years. Sahlgr. Hosp. 159/46, 2215/47 and 618/48.

In February, 1937, the patient was operated on for a »cyst» in the left half of the mandible. Microscopy revealed a tumour probably belonging to the group of so-called mixed tumours of the salivary glands. In December that year a gland was extirpated from the left side of the neck and showed metastases which exhibited the same histological characteristics as did the previously enucleated primary tumour. The patient then received roentgen therapy — altogether 1 800 r. Since then she felt well until a short time before re-admittance to hospital when she noticed a swelling of the jaw. The swelling gave moderate pain.

In January, 1946, the patient consulted Sahlgren's Hospital, where roentgen examination revealed a cyst-like lesion in the left angular portion of the mandible. The medial side of the lesion had no bony wall. A recurrence was suspected. See Fig. 1.

In February, 1946, the tumour was enucleated. Microscopy showed the characteristics of an adenocarcinoma of mucus-secreting type.

Microscopy: Re-examination (LINELL) showed the growth to be a typical mucus-secreting, cystic epidermoid carcinoma.

Fig. 1. Case 1. Intra-osseous mucus-secreting and cystic epidermoid carcinoma of the mandible.

In the autumn of that year a new glandular metastasis was observed: it was extirpated, and microscopy showed the same picture as before. Shortly afterwards there was a local recurrence extending posteriorly and cranially in the pharyngeal wall. Irradiation treatment was given without success.

Case 2. E. J. B. ♂ 60 years. Surg. Clinic, Lund. 438/48. (This case is included in the series published by LINELL in 1948.) All the premolars and molars except 7— in the right lower jaw had been extracted 20 years before. In 1930 he had a fixed gold-bridge fitted in which 7— was the posterior abutment. (He had had no wisdom teeth.) He complained of frequent discomfort and pain in the region of the abutment. In 1940 the bridge became loose and was replaced by a new one. In 1943 he developed a tender swelling in the lingual aspect of the left mandible. At the Radiological Dept., Lund, the swelling was conceived as an epulis and treated with irradiation, which, however, gave the patient no relief.

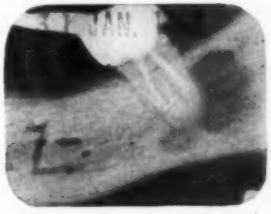

Fig. 2. Case 2.

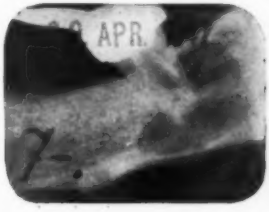

Fig. 3. Case 2. Re-examination 3 months later than fig. 2. Note the progression.

In January, 1947, the patient consulted his dentist: the roentgenogram revealed a periapical lesion adjacent 7— (Fig. 2). Expectant treatment with repeated roentgen control was decided upon. As the symptoms did not disappear, and as a slight increase in the size of the area destroyed was observed (Fig. 3), the bridge was removed and 7— extracted in September 1947, after which the pains disappeared.

Condition at the end of December 1947: No teeth behind 3— in right mandible. In the region of 7— the mandible was swollen to double its normal breadth.

Roentgen examination revealed an almost 2 cm × 1.5 cm cyst-like rarefaction extending down to the base of the mandible. The lingual side of the alveloar process had undergone almost complete destruction. The kind of tumour could not be definitely determined nor could adamantinoma or similar tumour be excluded.

In December the growth was enucleated.

Microscopy: Mucus-secreting, cystic epidermoid carcinoma, probably originated in ducts of the mucous glands (LINELL).

Complete resection was performed: the affected portion was excised radically. The regional glands were also enucleated. The jaws were fixed with splints, and after slightly more than 2 months the defect in the jaw was filled with a bone graft.

Microscopy of the resected specimen. »The excised part contained a large tumour, which seemed to be located mainly to the soft tissue parts of the medial aspect of the jaw. The tumour presented the same structural characteristics as did the material from the previously enucleated portion. Several infiltrating strands consisting of atypical, squamous epithelial formations containing numerous mucus-filled cells with many, scattered, mucus-filled cysts, lined with goblet cells were also to be seen. The stroma of the tumour consisted of sclerotic connective tissue with scattered inflammatory cells. The tumour grew medially out into the epithelial lining of the oral mucosa, which was infiltrated in patches. In the jaw bone was a large cavity filled with loose connective tissue. In some areas of the latter epithelial strand of the same type as already described were to be seen. The growth had not infiltrated deep into the bone. The bone cavity was surrounded by a layer of fairly delicate, new-formed, bone trabeculae. As far as the bone was concerned, the tumour had definitely been extirpated radically. Whether this was the case as regards the soft tissue parts of the medial aspect of the jaw could not be judged definitely, but in both directions there was a narrow zone of tumour-free tissue, so that, here, too, extirpation had probably been radical. The submandibular lymph nodes that were examined showed non-specific inflammation but no signs of metastases. The extirpated submandibular gland presented a normal appearance.

Diagnosis. Mucus-secreting, cystic epidermoid carcinoma. (LINELL.)

Case 3. A. J. H. ♀ 61 years. Seraph. Hosp. Surg. Dept. 2547/46. Ten years earlier the patient noticed a hard swelling in the region of 7—, 6—. She sought medical aid and the swelling was incised and »fluid drained». Afterwards it was about the size of a hazel nut. During the last 9 months it had, however, grown in size. The patient was therefore admitted to hospital.

Status on admittance in September 1946:

In the posterior part of the right mandible there was a slightly tender, walnut-sized, firm, elastic non-fluctuant tumour of the jaw. In the gum there was a small tumour with a fistula in its middle. S. R. 82. Hb. 69. Red count: 3.26 mill. White count: 4900. Wr. and Kahn's reactions: negative.

Roentgen examination. In the right angle and mandibular ramus there was a walnut-sized, multilocular, irregular, cystic lesion, the wall of which had been destroyed medially, but otherwise apparently survived in the form of a thin bony shell. The changes were probably ascribable to an adamantinoma. See Figs. 4 and 5.

Operation: Right mandibular resection. The tumour was greyish-red and soft. In several areas it had broken through the jaw lingually and involved adjoining soft tissue parts.

Fig. 4. Case 3.

Fig. 5. Case 3. Note the local destruction of the lingual portion of the mandible.

Microscopy: The extirpated tumour presented a picture suggestive of an atypical adamantinoma. In several patches it closely resembled epidermoid cancer, and in some patches it showed adenoid structures. There was no distinct seam of ameloblast-like structures. The tumour showed polymorphocellular and infiltrative growth.

Re-examination of the preparation (LINELL) revealed the tumour to be a typical mucus-secreting, cystic epidermoid carcinoma.

Discussion

As already mentioned, mucus-secreting, cystic epidermoid cancer develops primarily in the ducts of major salivary glands or in the ducts of the mucous and minor salivary glands in the oral mucosa and grows secondarily into the jaw bones. In all three of the cases reported the location of the growth, was, roughly speaking, one and the same, namely, in the angular portion of the mandible.

In all three cases the cyst-like lesion had broken through and partially or completely destroyed the lingual part of its bony wall. In cases 2 and 3 the operation report showed that the tumour had attacked the adjacent soft parts of the floor of the mouth. The recurrence in case 1 developed from these parts and grew posteriorly in the pharyngeal wall. In case 2 a swelling had been observed 4 years before in the lingual side of the mandible at the same site as the tumour now occupied, and was then thought to be an epulis. This form of cancer therefore seems to show a predilection for the oral mucosa in this region. In BOSSART's first case the growth was also first located in this area. The mucous and salivary glands lie in the submucosa and probably extend very near to the periosteum of the jaw bone in the area in question, where the mucosal lining is not very thick. On proliferation the tumour probably very soon reaches and destroys the cortical layer of the mandible and then penetrates deeper into the bone and at the same time involves an increasing area of the lingual aspect of the jaw.

That this kind of tumour can, as in BOSSART's second case, occur in the upper jaw is quite understandable. Especially in the posterior part of the gum, the many mucous and minor salivary glands should, at least theoretically, favour the arisal of mucus-secreting, cystic epidermoid carcinoma. Ordinary tumours of the mucous and salivary glands are also often seen in the upper jaw.

All three of the tumours occurred in women over 60 years of age. In none of the instances was the growth indolent. They were all fairly tender and all three of them caused moderate pain. That the pains disappeared in case 2 after extraction of the tooth, may probably be explained by the fact that, especially when chewing, the tooth exercised pressure on the tumor below it, and extraction of the tooth gave the patient relief.

In case 1 no information was available as to the rate of growth of the primary tumour although the first recurrence — after 9 years — seems to have grown fairly quickly. This was also the case with the second recurrence and with the metastases in the gland observed after the second enucleation. Case 2 apparently had a history of at least four years and, according to the patient's report, the tumour in case 3 had been

stationary for at least 9 years and then begun to grow again during the past nine months. Judging by the cases described then, this type of cancer grows very slowly but after enucleation it may — as in case 1 — distinctly show its malignant character. The histological preparations in all three cases show an at least patchy, infiltrative, non-encapsulated growth.

In these cases the roentgen picture is therefore perhaps somewhat surprising, because in all three of the cases the lateral view of the mandible shows a fairly well outlined and distinct rarefaction. In cases 1 and 3 the cyst-like lesion is surrounded by a distinct cortical margin like a benign cystic tumour. The tumour is capable of presenting a monolocular roentgen picture of a type similar to a radicular cyst or a certain type of adamantinoma and, when in an edentulous jaw, as in case 1, it may simulate the picture of a residual radicular cyst. It may also have a more irregular, lobulated outer contour — a polycyclic form — as in case 2. As illustrated in case 3, it may also assume the picture of a multilocular cyst formation, simulating a primordial cyst of corresponding type.

It is apparent from the descriptions of the roentgen pictures of these three cases that the bony wall of the medial side had undergone partial or complete local destruction. This mural destruction probably permits their distinction from odontogenic cysts, which usually expand buccally. An odontogenic cyst of the size shown in cases 1 and 2 would hardly have destroyed the cortical layer of the mandible to such an extent in this direction. The clinical course excluded the occurrence of an abscess. A remarkable observation was the strongly expansive growth in case 3. The thin cortical layer bulging down under the border of the mandible is the lower margin of the tumour protruding also bucally (see Fig. 3). The markedly bulgent wall has thus been reduced to a very thin bony shell.

This type of cancer is thus inclined to be invasive and destroy bony tissue, but it may at the same time grow very expansively. This expansive mode of growth distinguishes it from other forms of cancer, and roentgenologically its characteristics are practically the same as those of a benign tumour. Roentgenologically, it gives even a more benign picture than the closely related mixed tumours of mucous and salivary glands. The latter are generally described as being semi-malignant but not infrequently assume a distinctly malignant character, when the margin is as a rule less distinct, and the tumour very seldom has a cortical border. That mucus-secreting, cystic epidermoid cancer can, at least after insufficient enucleation or perhaps less suitable surgical intervention, also become definitely malignant is obvious from the course the disease ran in case 1.

It is apparent from the above that, if intra-osseous, the roentgen

picture of this form of cancer will hardly reveal the degree of malignancy of the lesion in the bone. Hence, a malignant or semi-malignant tumour may grow in such a manner as to present the roentgen picture of a benign tumour. Judging by the cases described, the type of cancer in question may behave like a benign tumour for many years but it can transform into a malignant form. In the cases examined it presented no characteristic roentgen picture. Roentgenographically this kind of tumour can obviously simulate both odontogenic cysts and other tumours of the jaw. In these cases, however, roentgenology was able to reveal the presence of a tumour but could not disclose anything definite as to its kind.

SUMMARY

The mucus-secreting and cystic epidermoid carcinoma generally presents a well outlined, cyst-like roentgen picture which does not permit definite roentgenologic differential diagnosis.

ZUSAMMENFASSUNG

Schleimbildende zystische Plattenepithelkrebse geben zumeist ein scharf abgegrenztes, zystenähnliches Röntgenbild, das keine sichere röntgenologische Differentialdiagnose erlaubt.

RÉSUMÉ

Les carcinomes pavimenteux kystiques mucipares donnent habituellement, aux rayons de Roentgen, une image d'aspect kystique bien délimitée qui ne permet pas, radiologiquement, un diagnostic différentiel certain.

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FROM THE RADIUM CENTRE FOR JUTLAND, AARHUS, DENMARK
(DIRECTOR: PROFESSOR CARL KREBS)

ESTROGEN THERAPY IN PROSTATIC CARCINOMA[1]

by

Poul E. Andersen

Up to the last 10 years cancer of the prostate was a disease with a very poor prognosis as well regarding cure as palliation and only the latest years seem to have brought some real progress in the therapy of this disease.

Even HARVEY noticed a relation between the functions of the testis and the prostate, observing that the prostates of bulls become smaller after castration. During the years 1893—95 WHITE tried treating enlarged prostatic glands by bilateral castration, but the treatment was abandoned after a few years for various reasons, what because most of those patients who sought medical help for prostatic disease at that time, required relief and alleviation more promptly than could be produced by operative removal of the testes, what because a careful pathologic differentiation between benign and malignant enlargement of the prostatic gland was not made as a routine. Finally at that period in the childhood of modern surgery the interest was focused more on the development of sheer surgical methods in the treatment of bladder neck obstructions.

1934 RANDALL revived the idea and tried to use castration in patients with prostatic carcinoma, and almost contemporaneously MUNGER irradiated the testes in patients with prostatic carcinoma and managed to get rather fair results which however were not published till 7—8 years later.

A few years later, about 1938, a good many different investigators began treating patients with cancer of the prostate by anti-androgen or especially estrogen therapy with female sex hormones. This use of the estrogenic hormones in the therapy of prostatic cancer which in the latest years also in this country with definite success has been tried as an anodyne and a cancer growth repressing therapy, is based mainly

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on a series of ingenious animal experiments by HUGGINS and assistants during 1940—41, which again were based on the work of KUTSCHER & WOLBERGS and the GUTMANS and their colleagues on the acid and alkaline phosphatases. The level of the serum acid phosphatase was found to be abnormally high in many patients with prostatic cancer, especially when bone metastases were present. After a long series of excellent animal experiments HUGGINS & HODGES examined the effect of castration and administration of androgenic and estrogenic hormones on the amount of serum acid phosphatases in patients with advanced, metastasizing cancer of the prostate and found that the amount of serum acid phosphatase decreased quickly after a bilateral castration or the administration of stilbestrol, while testosterone propionate produced an increase. Parallel with the decrease in serum acid phosphatase a considerable improvement in general condition followed, the pain was relieved, the symptoms of bladder neck obstruction decreased and patients who had been bedridden on account of their painful bone lesions, were often able to get up and to resume their normal activities. These results were soon confirmed by other authors (HERBST, GUTMAN, SULLIVAN & GUTMAN, KAHLE, OGDEN & GETZOFF, WATKINSON, DELORY, KING & HADDOW and others), and estrogen therapy of some kind is now a very essential part of the therapy in cases of prostatic carcinoma, especially in cases with metastases.

The foundation of HUGGINS & HODGE's use of castration and stilbestrol in cases of metastasizing prostatic cancer was partly the discovery by GUTMAN, SPROULE & GUTMAN in 1936 of the increased levels of serum acid phosphatases in these patients, partly a series of experiments carried out by HUGGINS & CLARK in senile dogs during 1940 in which they found that spontaneous cystic prostatic hyperplasia in these senile dogs underwent a rapid involution after castration or administration of estrogens. This relation suggested to them that cases of highly differentiated carcinoma of the prostate might also be sensitive to such antiandrogen therapy. Although such therapy had been attempted earlier with genuine estrone without success, it was now tried again with the very strong synthetic estrogens which DODDS and co-workers had produced in 1938, and with the said good results. So during the last ten years estrogen therapy — at least in cases of metastasizing prostatic cancer — has become almost the most important therapy in these cases. However it is not to be forgotten that there seems to exist an anaplastic type of prostatic cancer which responds only very insignificantly — if at all — to the estrogen therapy, and the other ways of treating this disease — extirpation, partial resection, roentgen therapy etc. — still have their field within the treatment, especially in those cases, in which the capsule has not been penetrated by the cancer.

Treatment by stilbestrol in relation to other forms of treatment of prostatic cancer

In modern estrogenic therapy practically only the synthetisized drugs: stilbestrol, hexestrol and dienestrol are used, of which stilbestrol seems to be the most effective substance (MORSON and others). Although this is applicable to almost every case of prostatic cancer, one is likely to advise and to attempt a radical operation in cases, in which the cancer is believed still to be within the boundaries of the prostatic gland itself, when no bone metastases are demonstrable by radiography, when the rectal exploration fails to reveal infiltration lateral to the prostatic gland and when the serum acid phosphatase is normal. Some authors (COLSTON & BRENDLER) claim that estrogenic substances are indicated as a preoperative treatment, and GUTIERREZ has published one case in which a prostatic carcinoma seems to be cured even on histologic examination by estrogen therapy, but nevertheless one must maintain that still it has not been proved sufficiently that these substances are capable of changing malignant prostatic tissue into benign, normal tissue and that they — as far as we know at present — only are capable of repressing the growth of the prostatic carcinomatous tissue. So in cases of a limited tumour without demonstrable metastases one must prefer an immediate radical operation and then perhaps, if it seems advisable, use stilbestrol as a postoperative procedure to prevent or at least delay the development of metastases.

The effect of stilbestrol on the bladder symptoms is very variable and is as a rule least pronounced in cases of a considerable enlargement of the prostate. Even if the mollifying effect on the prostatic cancer which is sometimes seen and which may be followed by shrinkage and some fibrosis, may effect that the bladder function becomes normal, transurethral, and more seldom suprapubic resections are often indicated whereas the purely palliative suprapubic cystostomias can be avoided except in cases in which carcinomatous invasion in the external sphincter results in incontinence, impending uremia etc.

Thus the principal use of the estrogens will be in cases of bone lesions which are usually very painful. In these cases the anodyne effect often by far surpasses the effect of roentgen therapy, specially with regard to rapid alleviation. In addition cases have been published in which complete regression of the bone metastases has been noticed (NESBITT, HUGGINS), but still the rule seems to be, that there is a constant slow progression with or without periods of stagnation or even rather considerable regression of metastases. Usually metastases of the lungs or lymph nodes behave in the same manner, but cases of total regression of lymph node metastases with histologic verification have been reported.

In the late stages of the disease in which sometimes a reactivation of the prostatic cancer with acceleration of growth sets in in spite of continued estrogen therapy, roentgen therapy of the bone lesions may be very useful even if the condition may be temporarily relieved by a drastic increase of the stilbestrol dosage.

Chemotherapeutics such as the nitrogen mustards, urethane etc. have been proposed as an adjuvant and the author has tried urethane in a few cases on account of its influence on the mitosis but the results have not been encouraging. The patients rapidly deteriorated, the pain was unchanged or even became worser, the serum acid phosphatase value increased rapidly and the patients died after a few weeks.

Administration

Usually the estrogen therapy is given by stilbestrol perorally in rather heavy doses, but, the optimal daily dosage can not be said to be settled yet. In the Anglo-American countries a daily dose of 15—20 mg, sometimes even 60 mg, is the most commonly used amount (Cox, Fergusson). In the patients from the Radium Centre, Aarhus, daily doses of 3—12 or 15 mg have been given, trying to find a dosage at which the serum acid phosphatase level was normal. This dosage has possibly and sometimes certainly been too small in some of the cases, because the more anaplastic prostatic carcinomas seem to cause only a comparatively slight increase of the serum acid phosphatase value even with bone lesions present. In fact sometimes we have found normal values in such cases, so that serum acid phosphatase values at or just below the upper limit for normal values in these cases in reality have been too high, and the author is of the opinion that we have to depress the serum acid phosphatase level as much as possible in cases of anaplastic prostatic carcinomas.

Finally it is not to be forgotten that it may be possible that those »reactivations» of the prostatic cancer which have been reported by most authors and which have also been noticed in the patients of the Radium Centre after a shorter or longer period of estrogen therapy, are due to the fact that the dosage now commonly used is too small, causing the growth-delaying effect to be insufficient or of a too short duration, while a greater dosage perhaps might produce an optimal, cancericide effect.

The clinical effect of the stilbestrol therapy consists partly of an improvement in general condition with alleviation of pain and of the symptoms of bladder neck obstruction and of the sciagraphic changes, partly of alterations in the blood chemistry and of the histology of the tumour. Within a few days, sometimes even within 24—48 hours, the patients are completely or almost completely without pain, feel quite well, regain their appetite and begin putting on weight. The frequent miction, especial-

ly the nocturnal, decreases, the residual amount in the bladder also often diminishes and following this there is cessation of urinary infection. After some months' treatment the prostate on rectal examination may be felt smaller and softer, but as a rule there is no great change, and a possible infiltration lateral to the prostate almost never disappears. Sometimes lymph node metastases diminish significantly or even disappear, and regression of pulmonary and mediastinal metastases has been reported (ALYEA, ALYEA & HENDERSON). Usually the bone metastases do not change significantly in the roentgenogram following the initial increase in calcification which is seen in almost every case, and small differences in the roentgenologic findings are difficult to evaluate because even small variations in the technique will have a great influence on the roentgenogram. The general impression of the numerous reports and our experiences are that the bone lesions in almost every case are growing slowly with or without periods of stagnation and often without influencing the general condition of the patient noticeably.

Changes in the blood chemistry. Usually there is a rise in the hemoglobin per cent and a fall of the sedimentation rate, as a rule parallel to the decrease in the serum acid phosphatase, so that the sedimentation rate may be used as a guide in determining whether the dose is to be increased or is to be considered sufficient. Thus practitioners and hospitals, in which determinations of serum acid phosphatase are not made as a routine, may have a valuable guide in the sedimentation rate. With the decreasing bladder neck obstruction follows a decrease of the blood urea if this has been increased which is a rather common finding in cases with obstruction of some duration. The serum acid phosphatase value decreases dependent on the dose given, while the serum alkaline phosphatase value usually rises in the beginning but later falls to normal values.

The histologic picture has been examined by several authors (HECKEL & KRETSCHMER, FERGUSSON, a. o.) by serial biopsies of the prostatic cancer. Apparently partly an alteration of the structure, partly cellular changes take place during the estrogen therapy. The adenocarcinomatous cases become more scirrhous and there is a very considerable decrease in the amount of cancer tissue per field of view in the microscope. The nuclei of the cancer cells diminish generally and pycnosis of the nuclei accompanied by vacuolization of the cytoplasm is often seen (SCHENKEN, KAHLE & BURNS). Histochemical reactions on the histologic preparations to demonstrate acid phosphatase show that the amount of acid phosphatase has diminished considerably during the estrogen therapy.

Side effects

With heavy dosage nausea and vomiting may occur, sometimes even giddiness, and these effects may cause the dose to be diminished. As a

rule after some time the mammary glands become enlarged and tender, especially the nipple may be very hypersensitive. These changes may be somewhat varying during the treatment and now and then finally disappear. An intense pigmentation of the areolar region is also seen as is a frequently considerable deposit of fat in the female regions of predilection such as the suprapubic region, the hips and the breasts, coincident with atrophy of the testes, loss of libido and potency in most of the cases.

A possibility which also has to be considered is the development of carcinoma of the mammary glands. During the last 2—3 years four cases have been published, reporting mammary cancer in male patients following protracted estrogen treatment of a prostatic carcinoma, first by ABRAMSON who reported the first histologically verified case; later at least 3 more cases have been published, among others by REIMAN-HUNZIKER and thus the possibility of creating a mammary cancer has to be remembered on the follow-up and control examinations of those patients which have been on the estrogen therapy for some time. However, the palliation and improvement in general condition gained by the stilbestrol therapy are so significant that these few scattered cases of mammary cancer which may have been caused by the stilbestrol therapy, do not justify an abandonment of the estrogen therapy.

Finally the patients now and then complain of precordial pain of the angina pectoris type, especially when a large dosage is given. More seldom are complaints of pains in the legs as in intermittent claudication. These pains are supposed to be vascular, and certainly one has to be cautious in using the estrogens in patients suffering from an angina pectoris, especially when remembering that many cases of this desease are benefited by the antagonistic substance testosterone (LESSER).

The patients

At the *Radium Centre, Aarhus* estrogen therapy has been used in the treatment of prostatic carcinoma since November 1944, up to the end of 1948 in 55 cases. The diagnosis has in every case been secured by at least 3 of the following criteria: histologic examination, roentgenologic demonstration of metastases, increased serum acid phosphatase level, rectal examination, clinical progress to death with or without post mortem examination. Cases which only were based on the findings at rectal exploration have not been included.

In addition to the estrogen therapy roentgen therapy has been used, several of the patients having received roentgen treatment before the estrogen therapy was adopted in November 1944. Roentgen treatment, however, has also been used after that date locally in cases of extremely persistent, painful bone metastases and in a few cases directed towards

the prostate. In evaluating the efficacy of the estrogen therapy the stilbestrol treated cases have been compared with a similar number of cases from the preceding years.

The average age of the patients when first admitted in this hospital has been 67.4 years (control group: 67.3 years). The distribution in age groups reveals nothing of interest and is to a large extent similar to that of the material reported by HULTBERG, the youngest patient being 51 years, the oldest 84 years. There is also a pronounced parallelism between the present material and the controls. On an average the duration of symptoms before the diagnosis was made had been 15.6 months (controls: 16.4 months), in those patients still alive c. 19 months, in those deceased c. 14 months. The average survival period from beginning of symptoms to death (in patients still alive: to 1. 1. 1949) has been 39.2 months, for the dead patients 36 months, for those still alive 47.5 months, while the average length of survival of the controls from the preceding years was only c. 23 months. Thus the survival period from the diagnosis was made, has been c. 2 years in the cases treated by stilbestrol, while the controls had only c. 7 months. This considerable lengthening of the survival period, which is now between 3 and 4 times as long as earlier, is even more striking and contrasting when you remember that every patient of the control material has died while still 28 % of the patients treated by stilbestrol are living, which means that in time this relation will be changed further in advantage of the present material. The final relation can only be evaluated when every stilbestrol treated patient has died, but even now it can be seen that the use of estrogens means a considerable gain in life time compared with the irradiation therapy. An investigation of the average length of survival for those patients who either had metastases on admission or developed metastases in the sequel, counting from the point of time, when their metastases were observed, showed a mean period of survival of 24.8 months. By way of comparison it may be mentioned that HULTBERG found only 12.9 months in a material treated by irradiation, while NESBITT & CUMMINGS report 11.3 months after castration and ROMANUS 13 months for 17 operatively castrated patients.

Our findings are in accordance with those of other authors as *e. g.* HUGGINS, CRANE & ROSENBLOM, NESBITT & PLUMB, FERGUSSON. Thus FERGUSSON finds an average period of survival from the diagnosis of 19.3 months in his stilbestrol-treated material, but only 9 months for his controls.

None of our patients has been alive for more than 4 years on the stilbestrol therapy solely at present, but this is caused by the fact that this treatment was adopted only in the end of 1944, but one of our patients has on irradiation therapy followed by estrogens been alive for almost 7 years, further 2 more than 5 years and one more than 4 years in spite

of wide-spread metastases, the last mentioned still being alive and in good condition. It may also be mentioned that 17 of our patients are still alive and on stilbestrol therapy.

Radiographically demonstrable metastases were found in 40 patients on admission or when diagnosis was made, while 6 of the remaining 15 had clinical signs of metastases consisting of bone pain, but no demonstrable bone lesions. 5 of these 15 patients developed roentgen-demonstrable lesions later on, while two died from coronary thrombosis and two from uremia, but still 6 patients remain, in whom we have cause to assume that the stilbestrol therapy may have prevented the development of metastases, at present for a mean period of 20 months.

Even at the very first survey of the cases it was evident that various types of clinical course were met with along these patients. Cases were found which were characterized by a history of short duration and rapid development of bone metastases (as to serum acid phosphatases vide infra), which were often the first symptom and the one which made the patient seek treatment — as a rule on account of »rheumatism» which might even be caused by a spontaneous fracture. Contrasting these cases were cases with a very long history of symptoms of prostatic hypertrophy, in which signs of cancer developed following years of urinary inconveniences with often several transurethral or suprapubic resections. Of course transitions between these extremes occurred, but especially the group of cases with a history of short duration and rapidly developed osseous metastases was very conspicuous, so these cases were examined more thoroughly. The group comprises 16 patients with a history of less than one year's duration who had also within one year after the beginning of symptoms roentgen-demonstrable bone metastases. While these 16 patients make c. 29 % of the present material, the control material was found to contain 33 % of this type of patients. The survival periods differ considerably as is seen in the following table, especially in the patients treated by estrogens. As will be shown later on other differences exist between these two types.

Therapy	Type of history	Duration of symptoms before admis.	Survival period from begin of symptoms	Surv. per. from admis.	Average survival period
Estrogens	short	9 months	24 months	15 months	c. 39 months
	intermed. and long	18.5 »	46 »	27.5 »	
Roentgen rays	short	8 »	13 »	5 »	c. 23 months
	intermed. and long	20 »	28.5 »	8.5 »	

Serum Acid Phosphatases

The serum acid phosphatases in the patients of the present material were determined by the GUTMAN & GUTMAN method. Only values above 4 units have been considered above normal. The serum acid phosphatase level was determined in 35 patients before the treatment by stilbestrol was started; 11 of these patients had no demonstrable metastases (*i. e.* by radiography, palpation etc.), and only two had a value above 4. One of these two had clinical signs of osseous metastases while the other patient had a value of 5 G. & G. units. In the remaining 24 patients in whom osseous metastases were demonstrated, the serum acid phosphatase value was above 4 in 21 patients. The remaining 3 cases were one patient with a very short history, one patient who had had a prostatectomy a short time before and one patient who was admitted in this hospital after stilbestrol therapy had been started in another hospital. In this case the serum acid phosphatase value increased during the irradiation therapy which was given at first here reaching a maximum of 34, but fell to normal during the following stilbestrol therapy.

The serum acid phosphatase level was followed during a longer period in 43 cases, respectively 32 patients with osseous metastases and 11 cases without demonstrable osseous metastases. In the latter 11 patients the value was kept below 4 for the whole treatment period. In 17 of the 32 patients with bone lesions we succeeded in bringing the phosphatase value below 4 and to maintain this more or less constantly during the whole treatment period, while in the remaining 15 patients the value was constantly or almost constantly increased, often at a very high degree in spite of big doses of estrogen substances. Thus we succeeded in acquiring normal serum phosphatase values in about 2/3 of all stilbestrol treated patients. In 9 patients of the formerly mentioned group with a short history the serum acid phosphatase was determined before the estrogen treatment was started. In 5 cases increased values were found, in one case the value was only slightly above normal, while in the remaining 3 cases the phosphatase level was normal in spite of very extensive bone lesions.

A certain relation seems to exist between the histologic character of the tumour and the serum acid phosphatase value (SULLIVAN, HERBERT), and the author has the impression that in many anaplastic tumours the serum acid phosphatase value may be normal or almost normal even in case of widespread metastases, while the more adenomatous and highly differentiated tumours tend to have markedly increased phosphatase values. The small number of patients in this material does not permit any safe conclusions on this point, but the author is strongly impressed that the shorter the history and the more anaplastic the tumour, the

more often a normal or only slightly increased serum phosphatase value is met, even in cases of widespread metastases, while on the other hand the longer the history, the more often the case is an adenocarcinomatous tumour, possibly starting from a prostatic hypertrophy, and the more frequent is a very considerable rise in the serum acid phosphatase. Even if the small size of the present material do not allow any safe conclusions on a possible relation between the histologic character of the tumour, its affectability by stilbestrol therapy and the length of survival, it is the author's impression that the cases of mainly adenocarcinomatous tumours of a rather high differentiation seem to have a longer period of survival and no doubt they respond far better to the estrogen therapy symptomatically.

The palliative effect of the stilbestrol therapy

While on account of the short period in which the stilbestrol therapy has been in use no case of 5 year survival on this therapy alone can be presented yet, it is however possible as already mentioned to record a considerable prolongation of the average survival period which is now at least 3 times as long as before the introduction of stilbestrol in the therapy, and what is almost more important to the therapist, there is usually a striking symptomatic effect of the treatment even in neglected and desolate cases.

Compared with the condition of the patient before the beginning of the stilbestrol therapy the effect was striking in a series of cases, while in other cases the effect was of a shorter duration and less pronounced and while still other cases showed almost no effect at all.

An examination of the effect on the general condition shows that in c. 1/3 of the patients there was a pronounced and lasting improvement of the condition; another 1/3 of the cases improved for a rather long time after which the symptoms again — often rather suddenly — were aggravated. In some of these cases the patient improved for some time following an increase of the dose, then a new relapse followed which usually rather rapidly was followed by the death of the patient. In 10 cases no definite improvement of the general condition was noticed, the condition being somewhat varying, sometimes a little better, sometimes a little poorer, but no real improvement for a longer period was obtained in these patients. Yet it is probable that the dosage in some of these cases has been too small, as these cases are most common among those treated during the first years. Thus at least in some cases an insufficient dose may be the explanation of the deficient effect. Finally 6 patients admitted at a moribund stage were treated for so short a period that no safe impression of the effect of the treatment could be obtained, but in no case a

deterioration of the patient was observed such as was seen in the urethane therapy.

The anodyne effect

While the irradiation therapy may bring the patient alleviation of the pain from bone metastases in some weeks the stilbestrol therapy was far more prompt in its effect on the pain which as a rule disappeared in 3 or 4 days following the initial dose of 10—15 mg daily. In a few cases the pain disappeared within 48 hours and in some cases the treatment had to be continued for a week or more before the relief was really striking. The ability of being out of bed and walking around was affected in the same way, and it has been most encouraging to see that disabled, bedridden and tormented patients in a few days were able to be out of bed and to walk around and resume their former life.

The weight was followed for a long period in c. 2/3 of the patients and in about 1/2 of them there was a considerable increase. Further 7 patients had an increase for some time which was followed by a decrease during relapse and terminally. In 5 cases the weight was constant and only in 6 cases there was a continual decrease of the weight. These patients were in a terminal stage on admittance. The increase of weight seen in the first group of patients was not insignificant; a gain of 10 kg or more was not uncommon at all, and in some cases a gain of 20 kg (or about 1/3 of the total weight of the patient) within a year was noticed.

The finding at rectal exploration was controlled during a longer period in 35 patients, but only in 5 cases — even after treatment for a long time — one felt sure that the carcinomatous prostate diminished and became softer, in short that there was a substantial improvement In 13 patients the findings were rather unchanged and in 17 patients a marked progression was found in spite of the stilbestrol still being given. This is the cause why we do not believe in the advantage of preoperative treatment by estrogens.

The amount of residual urine was measured in 11 patients during the first period of admission and was found to decrease in 10 patients, while it increased in the remaining case. On the whole there was a considerable improvement in the ability of emptying the bladder in most patients, and this was followed by a cessation of the urinary infection so commonly met with in these patients.

The effect on the bony lesions found in the radiograph was the well-known ebonization which was found in most cases. As a rule the osteosclerosis was very considerable and remained until death. The effect on the radiographically demonstrable lesions may be rather difficult to evaluate at the monthly or bimonthly follow-up as even small variations in the technique may change the appearance of the bone meta-

stases in comparison with the remaining, normal bone structures significantly, but as a whole the influence of the estrogen therapy on the bone lesions radiographically seems to be rather slight. Among our patients no bone metastases could be demonstrated in 13 cases and in 19 cases with bone lesions there was no follow up with radiographs. In the remaining 23 patients progression was found in 20 cases, in 3 of them, however, so that while some bone lesions disappeared, others and more numerous new lesions appeared elsewhere. The remaining 3 patients behaved as follows: in one patient the bone metastases at first progressed, but as the dosage was adjusted at a rather high daily administration, regression followed of all the radiographically visible metastases. A second patient also showed regression, while the third patient has shown only a dubious regression, but at least no further progression of the bone lesions so that the condition has to be regarded at least as stationary. The average period of survival of these three patients from the beginning of stilbestrol therapy is c. 3 $^3/_4$ years.

The blood

The sedimentation rate has been followed during a longer period or the whole treatment in 37 patients and in 20 cases showed a constant fall, while in 12 cases it was somewhat varying, usually at first falling and later on again rising indicating that the patient had reached a terminal stage. A rather close parallelism between the sedimentation rate and the serum acid phosphatase value during the stilbestrol therapy has been noticed, the serum acid phosphatase however reacting quicker to the estrogen therapy, while the sedimentation rate is trailing somewhat behind. The sedimentation rate may however, when there is no opportunity of following the condition of the patient by estimations of the serum acid phosphatase, be used as an excellent guide, as a falling or unchanged sedimentation rate can be taken as an indication that the daily dose of stilbestrol is sufficient, while an increasing sedimentation rate indicates progression of the disease and an insufficient therapy.

In most cases the hemoglobine has been somewhat up and down or usually falling on account of the increasing bone carcinosis. In 11 patients the hemoglobine was increasing.

The blood urea in most patients paralleled the bladder function, many patients being admitted with a beginning uremia which cleared up with the improved drainage following the »mollifying» effect on the prostate.

Thus the stilbestrol therapy has had a considerable palliative effect, the patients to a large extent becoming free from pain, regaining appetite and spirits and resuming a normal life, while the urinary inconveniences diminished and their whole condition became far mor endurable, just

as a large proportion of them stands a fair chance of living for a considerably longer period than with the previously used therapies. On the curative effect no safe conclusions can be made yet on the present material of patients, but nevertheless in some few cases regression of bone metastases has been observed and one seems entitled to hope that if the patient comes at a fairly early stage — even if beyond operability — it shall be possible to bring the prostatic carcinoma in a »neutral» stage, so that the patient may have an almost normal life and later on may die from another cause, without his life being shortened to any essential extent by the prostatic cancer.

SUMMARY

The author reviews the development of the hormonal therapy of prostatic carcinoma and reports a material of patients from the *Radium Centre, Aarhus*, Denmark. The patients which all were beyond operability, were treated with Stilbestrol in doses of 3—15 mg daily, using the serum acid phosphatase level as a guide.

The average survival period is now more than 3 times as long as in a control material from the preceding years and is about 2 years as against 7 months.

While it is dubious whether there is any curative effect even if in a few cases regression of the bony lesions has been obtained, the stilbestrol treatment has produced a considerable palliation in cases of bone metastases and has to be strongly recommended.

ZUSAMMENFASSUNG

Der Verfasser gibt eine Übersicht über die Entwicklung der hormonalen Therapie von dem Prostatakarzinom und berichtet über eine Patientsammlung der *Radiumstation Aarhus*, Dänemark.

Die Patiente, die alle inoperabel waren, wurden mit Stilböstrol in Dosen von 3—15 mg täglich behandlet, indem man den sauren Serumfosfatase-wert als Leitfaden benutzte.

Die durchschnittliche Überlebungsdauer ist jetzt mehr als dreimal so lang wie in einem Kontrollmaterial aus den vorhergehenden Jahren und ist nun c. 2 Jahre gegen 7 Monate früher.

Während es zweifelhaft ist, ob die hormonale Therapie eine kurative Wirkung hat, selbst wenn auch einige Fälle von Regression der ossösen Veränderungen erzielt wurden, muss man andererseits die bedeutende palliative Wirkung in Fällen von Knochenmetastasen stark hervorheben und die Verwendung der hormonalen Therapie empfehlen.

RÉSUMÉ

Ayant donné un aperçu du développement du traitement hormonal de cas de cancer de la prostate, l'auteur rapport sur les malades traités à *Radiumstation Aarhus*, Danemark.

Les malades, qui tous étaient inopérables, furent traités par stilbestrol en doses de 3—15 mg de jour, employant la serum phosphatase acide comme guide.

La survie moyenne a été plus que 3 fois plus long qu'en comparaison des malades des ans précédents et est maintenant c. 2 ans auprès de 7 mois.

Même si c'est incertain s'il y a aucun effet curatif, on a pourtant obtenu de regression des lésions osseuses, et l'effet palliatif a été très considerable, surtout en cas de métastases osseuses, voilà pourquoi il faut recommander l'emploi du traitement hormonal en cas inopérables de cancer de la prostate vigoureusement.

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FROM THE INSTITUTE FOR PATHOLOGY, PRETORIA, SOUTH AFRICA
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OSSEOUS CHANGES IN NEURAL LEPROSY[1]

Radiological Findings

by

James Barnetson

Papers on bone changes in neural leprosy are scanty. HIRSCHBERG and BIEHLER (1909) reviewed the literature prior to 1909. Important modern papers are those by TARCHINI (1925), HOPKINS (1928), CHAMBERLAIN, WAYSON and GARLAND (1931), MURDOCK and HUTTER (1932), KARASEFF (1936), OBERDOERFFER and COLLIER (1940), FAGET and MAYORAL (1944), and COONEY and CROSBY (1944).

General conclusions derived from this and other literature are: osseous changes in neural leprosy occur almost exclusively in small bones of hands and feet. The principal change is atrophy and disappearance of bone without productive changes unless secondary infection has occurred. Atrophy begins at distal margins of terminal phalanges but destruction may become greater in more proximal bones. Lesions are bilateral and are frequently stated to be symmetrical. Degree of bone change varies with duration of leprosy, extent of nerve involvement, age of patient, trauma, secondary infection and other factors. Radiological changes in neural leprosy are not specific. There is difference of opinion regarding occurrence of localised, regional or diffuse osteoporosis.

This paper records results of a radiological survey of bones of hands and feet of 107 neural lepers. All were Native adults and males predominated.

Early Cases

Cases were classified as »early» when external deformity was slight or absent. Duration of symptoms in this group varied from one to twenty

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Early Neural Leprosy Changes in Phalanges of Fingers

Fig. 1. Fig. 2. Fig. 3. Fig. 4. Fig. 5.

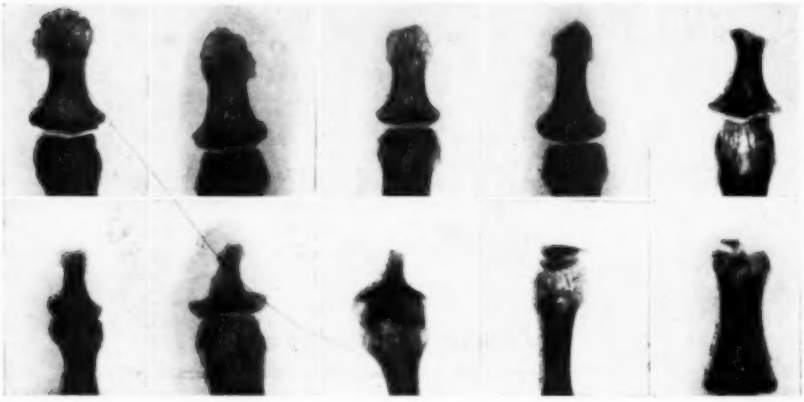

Fig. 6. Fig. 7. Fig. 8. Fig. 9. Fig. 10.

Fig. 1. Case 9650 — Notching on margin of tuft.
Fig. 2. Case 9911 — Early atrophy affecting tuft laterally with sliced-off appearance.
Fig. 3. Case 9679 — Atrophy affecting tuft centrally with flattened appearance.
Fig. 4. Case 8520 — Slightly more advanced atrophy of lateral side of tuft.
Fig. 5. Case 6247 — Tuft almost gone. Sliced-off appearance of distal end of shaft.
Fig. 6. Case 8109 — Tuft gone. Frayed appearance of end of shaft.
Fig. 7. Case 9845 — Disappearance of tuft and distal part of shaft.
Fig. 8. Case 8109 — Only base and proximal part of shaft remain.
Fig. 9. Case 6247 — Only base remains as flat button-like disc.
Fig. 10. Case 9901 — Only fragment of base remains. Fraying of distal margin of next phalanx.

years and degree of anaesthesia in hands and feet varied from almost nil to complete anaesthesia.

Investigation of such cases showed the radiological evolution of bone atrophy in neural leprosy to be as follows:

In hands and feet earliest changes occurred invariably on distal margins of termal phalanges as minute nicks (Figs. 1, 2 and 12). As these enlarged, the tuft lost its sharp outline and became frayed. If later atrophy affected tuft centrally its distal margin became flattened (Fig. 3), whilst if lateral margin was involved a sliced-off appearance resulted (Figs. 2, 4, 13 and 14). With further progress, tuft disappeared and phalanx consisted of base and part of shaft with frayed, notched or sliced-off distal margin or drawn-out appearance of shaft (Figs. 5—8, 15—17). Later,

Fig. 11. Fig. 12. Fig. 13. Fig. 14.

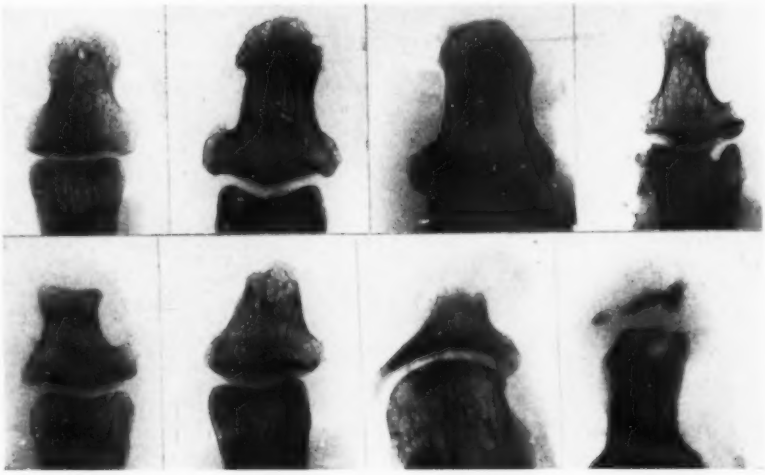

Fig. 15. Fig. 16. Fig. 17. Fig. 18.

Fig. 11. Case 9184 — Translucent area suggestive of enlarged nutrient foramen.
Fig. 12. Case 9343 — Notching on margin of tuft.
Fig. 13. Case 8203 — Atrophy of lateral margin of tuft.
Fig. 14. Case 8568 — Sliced-off appearance of tuft. Notch on distal margin of proximal phalanx.
Fig. 15. Case 9654 — Complete disappearance of tuft.
Fig. 16. Case 10031 — Disappearance of tuft and part of shaft.
Fig. 17. Case 8067 — Only base of phalanx and proximal part of shaft remain. Frayed appearance of distal margin.
Fig. 18. Case 8512 — Only fragment of base remains. Distal end of proximal phalanx shows apparent osteoporosis and periosteal reaction suggestive of secondary infection.

base of phalanx remained as a flat disc which eventually disappeared and process continued in more proximal bone (Figs. 9, 10 and 18).

Changes were nearly always bilateral but rarely truly symmetrical in the sense that corresponding digits on both sides were not always affected, and if affected lesions were rarely in same stage of evolution. Atrophy of bones of feet was usually more advanced than in bones of hands. No unequivocal case of diffuse osteoporosis was encountered but in a few instances prominent bone trabeculations indicated slight osteoporosis (Figs. 5, 10 and 14). Further lesions were punched-out areas in cortical bone of phalanges (Figs. 14 and 24) and radio-translucent areas suggestive of enlarged nutrient foramina (Fig. 11).

Fig. 19. Fig. 20. Fig. 21. Fig. 22.

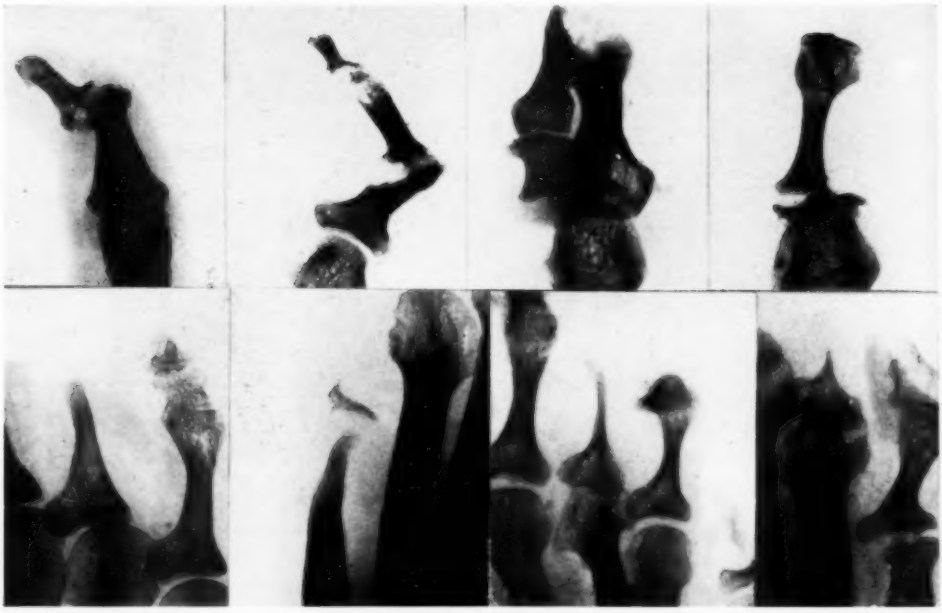

Fig. 23. Fig. 24. Fig. 25. Fig. 26.

Fig. 19. Case 8568 — Early atrophy of tip of distal phalanx. Absorption of bone at adjacent surfaces of distal interphalangeal joint.

Fig. 20. Case 9843 — Early atrophy of distal phalanx. Absorption of bone at adjacent surfaces of interphalangeal joints.

Fig. 21. Case 6247 — Atrophy of tuft of terminal phalanx. Absorption of bone at adjacent surfaces of proximal interphalangeal joint.

Fig. 22. Case 6247 — Complete atrophy of terminal phalanx. Only base of second phalanx remains. Proximal phalanx shows concentric atrophy and is fractured at base.

Fig. 23. Case 8998 — The two distal phalanges of this 3rd toe have disappeared. Proximal phalanx shows atrophy of head and concentric atrophy of shaft with drawn-out appearance.

Fig. 24. Case 8520 — The two distal phalanges of the 5th toe have disappeared. Only a fragment of proximal phalanx remains. Distal end of 5th metatarsal shows atrophy with pointed appearance. Note notches on lateral aspect of 4th metatarsal.

Fig. 25. Case 8109 — Atrophy and disappearance of distal phalanges. Concentric atrophy of 3 proximal phalanges shown.

Fig. 26. Case 9490 — Shows 4th and 5th toes. In 4th toe the two distal phalanges have gone. Proximal phalanx is represented only by base and proximal part of shaft which is markedly pointed. In 5th toe there is destruction of bone at adjacent surfaces of metatarso-phalangeal joint although distal phalanges are still present.

Fig. 27.

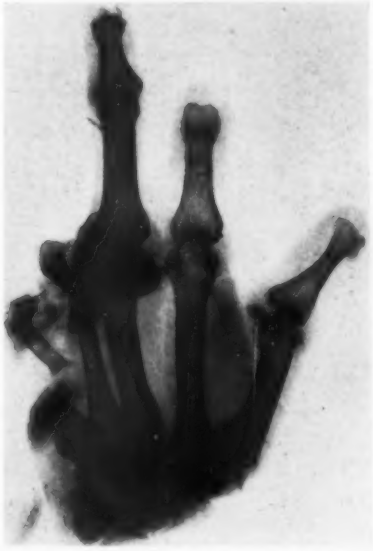

Fig. 28.

Fig. 27. Case 7874 — Several phalanges have disappeared. Absorption of both phalanges of thumb with subluxation of joint. Atrophy of 2 proximal phalanges of 1st finger at proximal interphalangeal joint with appearance simulating pathological fracture. Fraying of distal margin of proximal phalanx of 5th finger. Two small round blemishes (artefacts) are present.

Fig. 28. Case 9490 — Diffuse osteoporosis with thinning of cortices. Disappearance of several phalanges. Atrophy of bone at adjacent surfaces of metacarpo-phalangeal joints of 4th and 5th fingers with subluxation.

Advanced Cases

Cases were classified as advanced when moderate or marked external deformities of hands and feet were present. Duration of symptoms varied from 2 to 33 years and in nearly all cases anaesthesia was complete in both hands and both feet.

The principal lesion was proximal continuation of atrophy as in early cases. Atrophy was of pure type and periosteal reaction, osteosclerosis and sequestrum formation were rare in absence of secondary infection. Diffuse osteoporosis was seen in only 5 of 63 advanced cases (Figs. 28 and 29).

Atrophy proceded slowly and undramatically and usually without preceding osteoporosis from distal margins of terminal phalanges proximally until phalanges were completely absorbed, the process being then

Fig. 29.

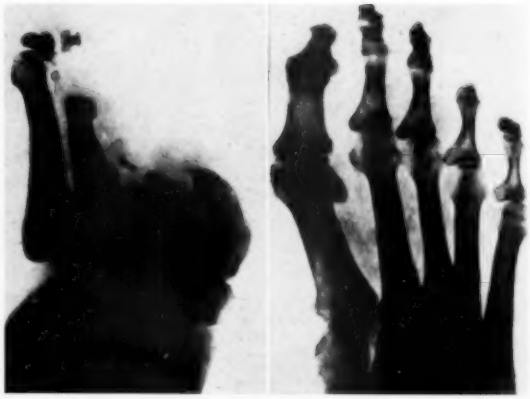

Fig. 30.

Fig. 31.

Fig. 29. Case 9292 — Diffuse osteoporosis with thinning of cortices. Disappearance of several phalanges and varying degrees of atrophy of those remaining. Marked concentric atrophy of proximal phalanx of 4th finger although cortex of this bone appears relatively dense.

Fig. 30. Case 5216 — Advanced changes in left foot with disappearance of all phalanges except those of big toe which remain as distorted fragments. Advanced atrophy of 3rd, 4th and 5th metatarsals. Apparent reactive new bone formation at bases of first 2 metatarsals. Changes in right foot are very slight.

Fig. 31. Case 7239 — Atrophy is more advanced in proximal than in distal phalanges and in relation to bone adjacent to all metatarso-phalangeal joints. Concentric atrophy with needle-like appearance of proximal phalanges of 3rd and 4th toes. Atrophy of distal ends of all metatarsals with drawn-out appearance in some.

Fig. 32.

Fig. 33.

Fig. 32. Case 2902 — Disappearance of several phalanges. Those remaining are distorted and drawn-out. Metatarsals show distortion and variation in shape and distal ends are drawn-out.

Fig. 33. Case 8568 — Early atrophy of 2nd phalanx of big toe. Disappearance of terminal phalanx of 2nd toe and of several phalanges of 4th and 5th toes. Concentric atrophy of proximal phalanges of 2nd, 4th and 5th toes. Absorption of bone at adjacent surfaces of metatarso-phalangeal joint of 3rd toe with pointed appearance of proximal part of proximal phalanx and distal end of metatarsal.

repeated in more proximal bones until whole digits disappeared (Figs. 23—33). Metatarsal bones were frequently affected (Figs. 24, 26, 30—33), but rarely metacarpals (Fig. 28). Involvement of tarsal bones was uncommon and there were no cases showing atrophy of carpal bones. Numerous varieties of deformity were produced depending on extent of involvement of bone, secondary infection, trauma and other factors.

Numerous cases characterised by slight atrophy in distal phalanges and gross destruction more proximally occurred in bone surfaces adjacent to interphalangeal or metacarpo-phalangeal joints and were associated with flexion deformities (Figs. 19—22, 26, 27 and 28). Subluxation was common. Distal bones although less affected then always showed some atrophy. Such bone destruction at adjacent surfaces of rigid insensitive flexed joints was due largely to repeated trauma.

In feet, advanced destruction of proximal bones was occasionally due to secondary infection but occurred more frequently without. Such destruction took place in bones adjacent to metatarso-phalangeal joints and was due (as has been indicated by various authors) largely to trauma in insensitive bones and joints caused by weight bearing. Subluxation was again frequent. As in hands when destruction was greater in more proximal bones distal phalanges of affected digits invariably showed evidence of absorption (Figs. 26, 31—33).

Lesions in advanced cases were always bilateral but rarely symmetrical. Lack of symmetry occasionally was striking (Fig. 30).

Pathological fractures are described in the literature on neural leprosy but were uncommon in our series (Fig. 22). An appearance closely simulating fracture was however frequent and was due to absorption of bone at surfaces adjacent to joints, interphalangeal or metacarpo- or metatarso-phalangeal (Fig. 27).

Mention is often made in the literature of »concentric atrophy». This is characterised by gradual narrowing of shaft of a short long bone and may terminate in pathological fracture or disappearance of distal end of bone with »drawn-out» appearance of proximal fragment (Figs. 23—26, 31—33). Concentric atrophy occurred fairly frequently in our series and several interesting points were demonstrated. The change was only seen in proximal phalanges, metatarsals and metacarpals. Distal phalanges, although frequently reduced to small fragments of bone, did not show true concentric atrophy. In several cases although concentric atrophy was marked, more distal bones of nearly normal calibre were present in the same digit (Figs. 31—33). In concentric atrophy dense cortical bone remained visible up to distal tip although medullary cavity was narrowed. In very advanced cases where bone had become needle-like in thickness and form it was still dense and compact (Figs. 25 and 31). The hand of patient 9292 (Fig. 29) was of special significance in this respect. It showed diffuse osteoporosis but with concentric atrophy of proximal phalanx of fourth finger. Cortex of this bone was thicker than those of its neighbours and the phalanx as a whole was denser than those of other digits. Concentric atrophy is therefore either associated with changes occurring mainly in cancellous bone and medulla or with subperiosteal new bone formation. The first alternative is more likely.

Involvement of joints was almost always associated with infection, or trauma as already described in bones adjacent to rigid flexed joints in fingers and in weight-bearing metatarso-phalangeal area of feet. Changes depended primarily on absorption of bony surfaces adjacent to joints and occurred without apparent inflammatory reaction. Other joint changes apart from flexion deformities were rare and of minor importance.

Clinical Findings in Patients

Registration No.	Age	Sex	Approximate Duration of Leprosy in years	Extent of Anaesthesia
2902	46	M	33	++
5216	50	M	18	++
6247	31	F	15	++
7239	27	M	11	++
7874	45	F	14	++
8067	25	F	7	++
8109	31	F	12	irregular
8203	30	M	20	»
8512	20	F	6	»
8520	23	M	10	++
8568	35	F	10	++
8998	44	M	7	slight
9184	23	M	4	hands +
9292	68	F	17	++
9343			not available	
9490	62	F	10	++
9650	50	F	2	slight
9654			not available	
9679	16	F	3	slight
9843	19	M	7	++
9845	42	M	4	irregular
9901	16	M	4	hands +
9911	55	M	3	hands +
10031	21	M	1 1/2	slight

++ = Anaesthesia complete in both hands and both feet.

Acknowledgements

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This paper has been abstracted from a portion of a thesis accepted by the University of Pretoria for the degree of M. D.

SUMMARY

This paper records results of a survey of radiological changes in bones of hands and feet of 107 adult Native neural lepers divided into an early and an advanced group.

In early cases radiological evolution of bone changes is described and illustrated. In advanced cases various anomalies are described and illustrated.

ZUSAMMENFASSUNG

Diese Arbeit gibt eine Übersicht der röntgenologischen Veränderungen der Hand- und Fussknochen bei 107 erwachsenen Eingeborenen mit Nervenlepra, auf eine Gruppe von Frühfällen und eine von fortgeschrittenen Fällen verteilt. Bei Frühfällen wird die röntgenologische Entwicklung von Knochenveränderungen beschrieben und veranschaulicht. Bei fortgeschrittenen Fällen werden verschiedene Veränderungen beschrieben und veranschaulicht.

RÉSUMÉ

Dans cet article sont relatés les résultats d'une étude portant sur les altérations d'ordre radiologique observées au niveau des os des mains et des pieds de 107 indigènes adultes, atteints de lèpre nerveuse et divisés en deux groupes, celui des cas au début et celui des cas avancés. Dans le premier groupe l'évolution radiologique des modifications osseuses est décrite et illustrée. Dans le second, diverses anomalies sont également décrites et illustrées.

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FROM THE INSTITUTE FOR PATHOLOGY, PRETORIA, SOUTH AFRICA
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OSSEOUS CHANGES IN NEURAL LEPROSY[1]

Correlation between Histopathological and Radiological Findings

by

James Barnetson

The literature contains few articles on histopathological investigations of bones in neural leprosy. HIRSCHBERG and BIEHLER (1909) reviewed the literature prior to 1909. HARBITZ (1900, 1910) described active osteoclastic absorption of bone, depressions on surface of bone reaching deep into bone substance, and absence of leprous osteomyelitis, periostitis or lepra bacilli in bone. HÄUPL (1930) mentioned somewhat similar changes and DE JOSSELIN DE JONG (1934) investigating tarsal bones of a neural leper stated that cortex and spongiosa contained very few and very small bone trabeculae irregularly distributed in an excess of fatty tissue. Periostitis is apparently uncommon in neural leprosy (HARBITZ 1910, TARCHINI 1925, CHAMBERLAIN, WAYSON and GARLAND 1931, KARASEFF 1936).

In the present investigation histological preparations of bones showing radiological changes of neural leprosy were made. These changes included fraying of distal ends of terminal phalanges, concentric atrophy of phalanges, various other deformities and diffuse osteoporosis. Bones investigated were obtained from feet removed at post mortem or amputated for various reasons.

It was found much more difficult to trace the histopathological evolution of bone changes than the radiological. Enough preparations were examined however, to venture an opinion on this matter.

In sections of normal phalanges of toes small gaps may occasionally be seen in the cortical bone and are usually filled with connective tissue. In our early neural lepers the first change appeared to be enlargement and increase in number of these gaps particularly along distal margins of phalanges. The gaps were filled with connective tissue continuous with

[1] Submitted for publication Febr. 16, 1950.

Fig. 1.

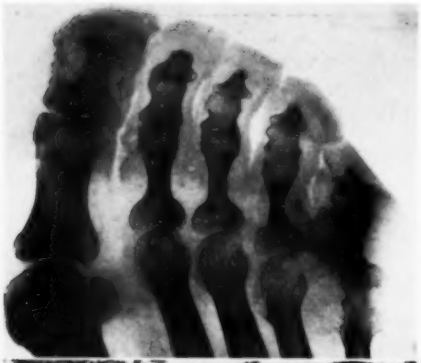

Fig. 3.

Fig. 2.

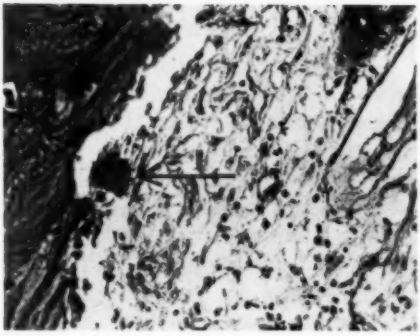

Fig. 4.

Fig. 1. Case 6239 — Anterior part of foot.
Fig. 2. Case 6239 — Distal phalanx of second toe × 37, showing cortical layer with gap containing connective tissue.
Fig. 3. Case 6320 — Anterior and middle parts of foot.
Fig. 4. Case 6320 — Base of fifth metatarsal × 127, showing myxomatous change and slight fibrosis of marrow. A small osteoclast can be seen.

periosteum and marrow. In preparations from later cases the bone marrow had become myxomatous in appearance both macroscopically and microscopically. At the same time it underwent fibrosis until in late stages little or no fatty marrow was present. In our preparations osteoclasts were rarely found. As it is generally accepted that bone absorption is invariably osteoclastic in mechanism this finding was unexpected. Bone atrophy in neural leprosy is however very slow, suggesting that osteoclasts may be extremely scanty or that the process may develop with periods of activity and quiescence. In very advanced cases, cancellous osseous tissue

Fig. 5.

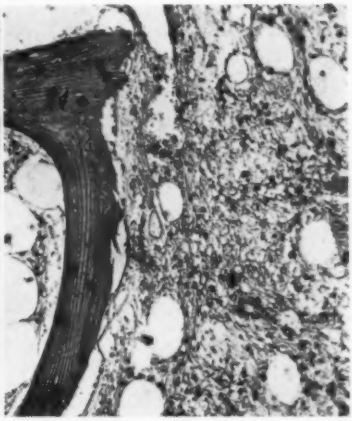

Fig. 6.

Fig. 5. Case 7693 — Anterior part of foot.
Fig. 6. Case 7693 — First metatarsal × 80, showing fibrosis of marrow. Moderate number of lymphocytes and plasmacells are present.

frequently had disappeared and the bone itself consisted of thick cortical bone with a narrow medullary cavity containing fibrous tissue.

All patients were adult Natives and all were neural lepers except Case 6239 who showed mixed lepromatous and neural lesions.

Case 6239 (Fig. 1). Roentgen examination showed early atrophic changes of all terminal phalanges with fraying of distal margins. There was narrowing of 5th metatarsophalangeal joint space with bone erosion suggestive of septic arthritis. Sections were made of terminal phalanges of the four medial toes. Histological changes which were similar in all these bones were as follows: The cortical bone was dense, of normal width and was well-formed up to distal margin but contained several abnormally large gaps. These gaps were larger and more numerous along the distal margin where fraying was evident radiologically (Fig. 2). They represented breaks in continuity of cortical bone, and were filled with connective tissue continuous with periosteum and bone marrow. Cortical bone at edge of gaps was smooth and showed no active osteoclastic activity. The cancellous bone showed no significant changes and osteoblasts were scanty. The bone marrow showed a few small areas of fibrosis and arterioles in these areas showed thickening of media and intima. No osteoclasts were seen.

Case 6320 (Fig. 3). This foot showed gross deformity and all phalanges had disappeared. Metatarsals showed advanced atrophic changes and 1st, 2nd, 3rd and 4th remained as short fragments with distal pointed ends. The 5th was less shortened and its distal end was drawn-out and rounded. Tarsal bones and proximal parts of metatarsals showed diffuse osteoporosis. Postero-inferior aspect of calcaneus was dense and sclerotic due to new bone formation resulting from secondary infection, associated with a large perforating ulcer on the heel.

Fig. 7. Case 6381.

The base of 5th metatarsal (Fig. 4) was examined histologically and changes were as follows. Cortical bone was dense but varied in width, some parts being distinctly narrower than normal. A few gaps containing connective tissue were present. Trabeculae of cancellous bone were of normal size and appearance and some were lined by osteoblasts. Bone-marrow showed marked generalised myxomatous change and early fibrosis, the connective tissue being well-formed but of loose texture. Blood vessels of marrow were dilated and engorged but there was no thickening of their walls. A few small collections of lymphocytes and plasma-cells were noted but there was no evidence of acute inflammation. Osteoclasts lying in Howship's lacunae were present. They were, however, very scanty and were confined to bone immediately underlying articular cartilage.

Case 7693 (Fig. 5). All phalanges of big toe had disappeared. First metatarsal had atrophied and was about half normal length. Its distal end tapered to a blunt end. In 2nd toe the two distal phalanges had disappeared and proximal phalanx showed atrophy of head with fraying of distal margin. In 3rd toe there was absorption of bone at adjacent surfaces of proximal interphalangeal joint. Lateral side of head of 5th metatarsal showed notching.

Sections were made of tip and base of 1st metatarsal and of distal end of proximal phalanx of 2nd toe. In 1st metatarsal cortical bone was narrow. Haversian canals were larger than normal and contained loose connective tissue and blood vessels. Cancellous

Fig. 8. Case 6381 — Phalanx of fourth toe × 13. There is atrophy of cancellous bone although cortex is thick. Marrow cavity contains connective tissue.

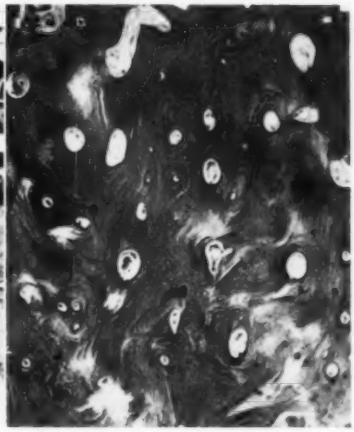

Fig. 9. Case 6381 — Distal end of fifth metatarsal × 27, showing dense sclerotic bone.

Fig. 10. Case 7590 — Anterior and middle parts of foot.

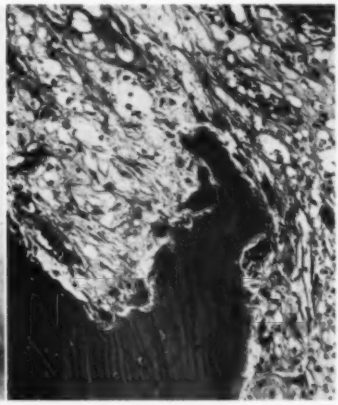

Fig. 11. Case 7590 — Base of third metatarsal × 100. Myxomatous change and fibrosis of marrow. Numerous osteoclasts in Howship's lacunae are present.

bone was of normal structure and trabeculae were not lined by osteoblasts. The marrow showed generalised myxomatous change and fibrosis (Fig. 6). Moderate numbers of lymphocytes and plasma-cells were present. Blood vessels were normal and no osteoblasts were detected. In proximal phalanx of 2nd toe cortical bone varied in thickness and gaps were present especially along distal margin. Trabeculae of cancellous bone were of normal size and there was generalised fibrosis of marrow. No osteoclasts were found.

Case 6381 (Fig. 7). Showed a large variety of changes. In big toe only fragments of phalanges remained. Head of 1st metatarsal had been absorbed and distal extremity tapered to a rounded end. Atrophic changes were present in phalanges of 2nd toe and 2nd metatarsal showed a sharp spur (probably non-leprous in origin) on medial aspect near base. There was absorption of bone at adjacent surfaces of metatarso-phalangeal joints of 2nd, 3rd and 4th toes with some bony ankylosis in 2nd and 3rd. In 4th toe only a thin sliver of proximal phalanx remained and distal end of metatarsal was atrophied and showed »a drawn-out» appearance. In 5th toe all phalanges had disappeared and only proximal part of metatarsal remained, its distal end being drawn-out to a fine point.

On dissection bones of this foot showed abnormalities of size and shape and a pitted appearance of distal margins of most distal bones in relative toes. Fourth and 5th metatarsals instead of narrowing to a point as suggested by roentgen examination showed side-to-side flattening of shaft which thus resembled a knife-blade in appearance. Phalanx of 4th toe showed concentric atrophy. Sections were made of several bones. Representative changes were found in remaining phalanx of 4th toe and distal part of 5th metatarsal. Phalanx of 4th toe (Fig. 8) showed, in the area which had undergone concentric atrophy, complete absence of cancellous bone although cortex was thick and dense. The medullary cavity was very narrow and contained fibrous tissue in place of fatty marrow. At base of phalanx cancellous bone was present. No osteoclasts were found. Microscopic examination of distal portion of 5th metatarsal (Fig. 9) showed that it consisted of dense cortical bone without evidence of osteoporosis or osteoclastic activity.

Case 7590 (Fig. 10). Most phalanges had disappeared. Remaining phalanges and metatarsals showed gross atrophic changes with resulting deformities. There was generalised diffuse osteoporosis with some irregular new bone formation.

All bones in the foot were examined histologically and changes were fairly uniform. There was thinning of cortical bone. Trabeculae of cancellous bone were slender and fairly numerous osteoclasts were present in Howship's lacunae. (Fig. 11.) They were most numerous in bone underlying articular cartilage and were also present immediately under the periosteum. Bone marrow was myxomatous in appearance and showed early fibrosis. Focal collections of neutrophil leucocytes in several bones and engorgement of blood vessels of marrow indicated active acute inflammation due to secondary infection.

Discussion

Histopathological examination of bones showing radiological changes of neural leprosy suggest the following correlations. Fraying of distal margins of bones is associated with breaks in continuity of cortical bone. The gaps are filled by connective tissue extending from periosteum to marrow. In cases of gross deformity when no diffuse osteoporosis is visible radiologically, cortical bone remains dense and of normal width up to distal margins of bone. When diffuse osteoporosis exists cortical bone is narrowed and evidence of active osteoclastic activity can usually be found. In

concentric atrophy cancellous bone undergoes absorption and marrow cavity is greatly reduced in width. Cortical bone remains however intact.

Other observations were: active osteoclastic absorption of bone cannot always be detected. Probably on account of the extreme chronicity of bone absorption in neural leprosy osteoclasis occurs either intermittently or on such a slight scale that osteoclasts are strangely scanty.

The cause of myxomatous change and fibrosis of bone marrow which appears to increase in severity with extent of bone change is at present unknown.

Acknowledgements

I am indebted to Dr. A. R. Davison of the Westfort Leper institution, Pretoria, for access to the material and to Mrs. C. van Niekerk for translation from the Norwegian.

This article has been abstracted from part of a thesis accepted by the University of Pretoria for the degree of M. D.

SUMMARY

This paper records results of study of radiological and histopathological changes in bones of feet of five South African Native Lepers, four being neural cases and one mixed lepromatous and neural.

Histopathological changes in bones in different stages of the disease are described and correlations are made between radiological and histological abnormalities.

ZUSAMMENFASSUNG

Diese Arbeit berichtet über eine Untersuchung der röntgenologischen und histopathologischen Veränderungen der Fussknochen bei fünf südafrikanischen Eingeborenen mit Lepra, nämlich vier Fällen von Nervenlepra und einem von gemischter Nerven- und Knotenlepra.

Die histopathologischen Veränderungen der Knochen in den verschiedenen Stadien der Krankheit werden beschrieben und die röntgenologischen und histologischen Krankheitsbilder zu einander in Beziehung gesetzt.

RÉSUMÉ

Dans cet article sont étudiées les altérations radiologiques et anatomo-pathologiques des os des pieds chez cinq lépreux indigènes de l'Afrique du Sud, quatre étant atteints de la forme nerveuse de la maladie, et l'un de sa forme mixte, à la fois tubéreuse et nerveuse.

L'auteur décrit les lésions histologiques à différents stades de l'affection et établit les corrélations entre les anomalies radiologiques et histologiques.

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FROM THE 1ST DEPT. OF DIAGNOSTIC RADIOLOGY OF SÖDERSJUKHUSET, STOCKHOLM, SWEDEN (HEAD: DOCENT G. JÖNSSON). IN COOPERATION WITH THE 2ND MEDICAL CLINIC OF SÖDERSJUKHUSET, STOCKHOLM (HEAD: PROF. G. NYLIN)

THORACIC AORTOGRAPHY IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS BOTALLI[1]

by

Bror Brodén, Gunnar Jönsson and *Johan Karnell*

A surgical intervention is nearly always indicated in patent ductus arteriosus. If the operation is performed at an early stage it can prevent heart failure and bacterial endocarditis, the commonest complications, and gives a better result than can be expected after a complication has manifested itself. It is therefore of considerable importance to make an early diagnosis. Many cases of patent ductus arteriosus yield typical auscultatory signs, and the condition can thus be readily diagnosed. In quite a number of cases, however, it is not possible to detect a patent ductus by means of the ordinary clinical methods of examination. These cases often remain undetected for a long time or can even fail to be diagnosed correctly at all, and the patients thus come for treatment either too late or not at all.

For the past two years we have been submitting patients with a patent ductus to thoracic aortography. Our report on the results we have obtained with this method will be preceded by a brief description of the anatomy, pathophysiology and clinical diagnostics in patent ductus arteriosus.

Anatomy

During fetal life, the ductus arteriosus is a normal vascular pathway between the pulmonary artery and the aorta. It usually becomes obliterated during the first few weeks of life but a delay in the obliterating process until the age of one year sometimes occurs as a normal variation. A persisting ductus arteriosus may occur as an isolated de-

[1] Submitted for publication May 2, 1950.

formity or in combination with other malformations, the commonest of which are coarctation of the aorta and tetralogy of Fallot.

The persisting ductus arteriosus is a short vessel connecting the aorta with the pulmonary artery at the spot where the latter divides into its two main branches, or with the left branch. The aortic end of the ductus is wider than the pulmonic end. There is nearly always a local dilatation in the aorta, around the base of the ductus. This dilatation was described for the first time in 1890, by THOMA, under the term »traction aneurysm». In many cases, the aorta and pulmonary artery are situated very close to one another and are in direct communication through a fistula-like opening. An extremely short ductus of this kind was reported by KEYS and SHAPIRO, in 10 out of 60 cases, in their survey of postmortem records. The same authors stated, as other investigators (STEINBERG, GRISHMAN & SUSSMAN, TAUSSIG) have also mentioned, that the ductus is very rarely longer than 1 cm. The diameter of the ductus (and by this is meant the shortest diameter, close to the pulmonary artery) shows much variation. According to TAUSSIG, it is 0.5—0.7 cm in the majority of cases. In our experience, however, cases with a diameter of more than 1 cm are not uncommon. The statements in the literature regarding the length and width of the ductus are based on observations made in connection with postmortem examinations, and operations. The autopsy findings are the more reliable of the two, seeing that the internal length and diameter of the ductus can be measured direct. Consideration must, however, be paid to the fact that the measurements obtained in the postmortem-contracted specimen are smaller than they are during life, when the vessel is distended with blood under arterial pressure. At an operation, the outer length and width of the ductus can be measured and the inner measurements are thus only obtained indirectly. As the wall of the ductus is not equally thick in all individuals, and its thickness is difficult to estimate with exactitude at an operation, this kind of indirect calculation of the inner measurements of the ductus is extremely precarious.

The Course of the Circulation

During fetal life, the greater part of the blood flowing in the pulmonary artery is shunted to the aorta through the ductus arteriosus. When the pulmonary circulation comes into function, immediately after birth, this blood passes through the pulmonary blood vessels and the flow of blood through the ductus ceases. As the individual continues to grow, the pressure in the systemic circulation gradually becomes higher than in the pulmonary circulation. If the ductus arteriosus is not obliterated blood starts to flow through the persisting ductus from the aorta

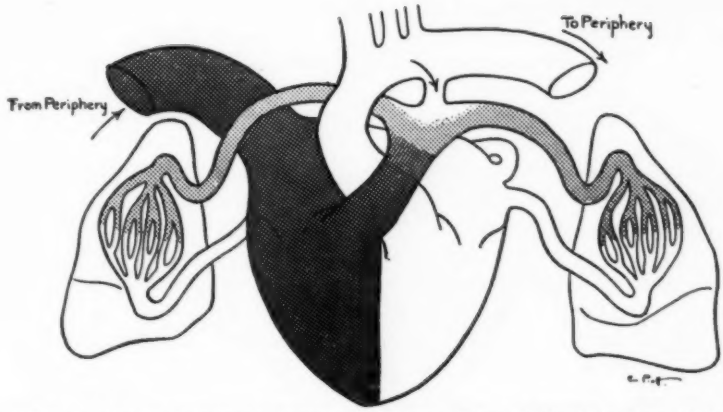

Fig. 1. The circulation in patent ductus arteriosus. Arterial blood is shunted from the aorta, through the patent ductus, to the pulmonary artery. (After EPPINGER, BURWELL and GROSS.)

to the pulmonary artery, owing to the difference in pressure (fig. 1). The amount of blood thus shunted may be considerable. EPPINGER, BURWELL & GROSS calculated, on the basis of a few cases with a very wide patent ductus, that 45—75 per cent of the aortal blood was shunted to the pulmonary artery. The pressure in the pulmonary artery increases to a considerable degree in many cases. Owing to the abnormal circulation and the disturbance in the blood pressure an increased strain is placed upon the heart, with hypertrophy and dilatation as the result. If the ductus is narrow, and the amount of blood shunted is small, there is often no evidence of increased strain on the heart at all.

Clinical Diagnosis

The most characteristic clinical sign in patent ductus arteriosus is *the continuous murmur*, which is produced by the flow of blood through the ductus. In many cases, however, the murmur is not continuous but consists, instead, of two distinct components, a systolic and a diastolic. In children, in whom the difference in pressure between the two circulatory systems is lower than in adults, a systolic murmur is often the only sound to be heard, possibly due to the fact that the flow of blood through the ductus is not continuous. It has also been known for a long time that a patent ductus can exist without producing any murmur. *From the aspect of the differential diagnosis, it is important to bear in mind that murmurs similar to that heard in patent ductus arteriosus may*

also be present in connection with other conditions, as in cases of aortic stenosis and insufficiency, rupture of a sinus of Valsalva into the right ventricle and congenital aortic septal defect (LEVINE; TAUSSIG; JÖNSSON, BRODÉN, HANSON & KARNELL; DODDS & HOYLE, and others).

The shunting of blood from the aorta to the pulmonary artery can be established by heart catheterization and blood gas analysis. An interarterial shunt can be demonstrated with the aid of this method, if it is established that there is a higher concentration of oxygen in the pulmonary artery than in the right ventricle. If, however, the shunt is inconsiderable, the difference in the oxygen concentration is sometimes so slight as to fall within the limits allowed for the normal variations in venous blood. An oxygen analysis, however, does not disclose *the site* of the abnormal communication between the vessels. Intracardiac measurement of pressure in the pulmonary artery and in the right heart chambers furnishes valuable information, but a sure diagnosis cannot be based on the pressures thus determined. In cardiac catheterization, the catheter can sometimes be inserted through the ductus and out into the aorta, and an unequivocal diagnosis is thereby obtained (KARNELL, JÖNSSON & BRODÉN, 1950).

A *roentgen examination* reveals the secondary anatomic changes, namely, enlargement of the heart and dilatation of the pulmonary artery, to the extent that they are present, but these observations are no more pathognomonic of patent ductus arteriosus than are the pathologic pulsations in the pulmonary artery known under the name of hilar dance. The ductus itself, which is situated in or close to the mediastinum, cannot be seen, except in the very rare cases where the ductus wall contains calcium deposits.

Angiocardiography has been used in so many cases of patent ductus that its value can now be judged fairly accurately. GRISHMAN & SUSSMAN, who have had wide experience of the angiocardiographic method in patent ductus arteriosus, wrote as follows in 1947: »Practically all cases of this condition which we have studied with the aid of angiocardiography revealed an abnormality in the outline of the aorta, not encountered in normal individuals or in other cardiac abnormalities, consisting of an apparent localized dilatation of the descending aorta or its anterior aspect just beyond the isthmus. The changed segment varies in size and shape from a localized bulge to a uniformly dilated segment. This appearance is probably due in most cases to the infundibulum of the ductus, although occasionally it may represent a traction aneurysm of the aorta caused by the ductus. The appearance, however, is not pathognomonic. Traction on the aorta from any cause will produce the same abnormality.

Because in the presence of a patent ductus, blood is shunted from

the aorta to the pulmonary artery or its left branch, it was anticipated that the ductus itself might be visualized or that there might be prolonged or renewed visualization of the pulmonary arteries. Neither expectation has been realized; on rare occasions a vascular structure has been seen which might have been the ductus proper, but its position in a maze of other vascular structures prevented identification. Prolonged or renewed visualization of the pulmonary artery was seen in a few cases, but the slight change in the density of this structure was no greater than might be present in any series of roentgenograms and the finding was therefore interpreted with caution. Presumably, clear visualization is impossible because the contrast medium in the pulmonary artery becomes too diluted when it is reshunted through the ductus.»

Thus, according to these investigators, the demonstration of a localized dilatation of the aorta (THOMA's »traction aneurysm») can cause the presence of a patent ductus to be suspected but does not constitute a sure proof of its existence. The renewed visualization that can be observed in some cases of patent ductus in our opinion possesses little diagnostic value. The phenomenon can also occur in interventricular septal defect and in conditions where there is an abnormal communication between the ascending aorta and the right ventricle or pulmonary artery (aneurysm in a sinus of Valsalva with rupture into the right ventricle, congenital septal defect).

Angiocardiography is therefore an unsuitable method for investigating a patent ductus arteriosus. For an examination of an interarterial communication between the aorta and the pulmonary artery it is necessary to inject the contrast medium into the aorta. We have previously stressed this fact, and have shown that a sure diagnosis can be made with the aid of *thoracic aortography*. In an article in this journal in 1948, published in collaboration with HANSON, we described two cases of patent ductus that had been examined by thoracic aortography. We were able to demonstrate that the contrast medium passed from the aorta to the pulmonary artery and that the interarterial communication was a patent ductus. In a patient who had an abnormal anastomosis between the aorta and the conus arteriosus or pulmonary artery (finding at operation), observations were made at an aortographic examination that could very well be put down to the malformation in question. Because of our observations in these first few cases we considered that there was some justification for continuing to investigate the value of thoracic aortography as a method of examination in patent ductus. We therefore used the method irrespective of whether the clinical diagnosis was regarded as definitely established or not.

We have recently published in this journal a detailed description of the *technique* of thoracic aortography, its risks and ways of avoiding

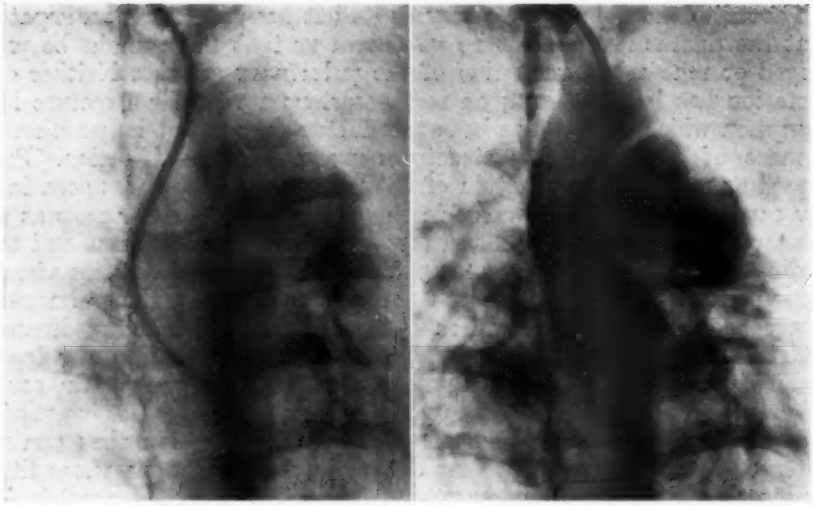

Fig. 2. Fig. 3.

Figs. 2 and 3. A woman, aged 27. Thoracic aortography. Contrast medium injected through a catheter. A large amount of contrast passed through the patent ductus, from the aorta to the pulmonary artery. At the operation the diameter of the ductus was estimated to be 0.7 cm.

them, and we therefore refrain from repeating them here (BRODÉN, HANSON & KARNELL 1948, JÖNSSON 1949, BRODÉN, JÖNSSON & KARNELL 1949).

Material

Adults

Thoracic aortography was used in 14 adult patients with patent ductus arteriosus. Thirteen of them were operated on. The diagnosis was verified at operation, and the anomaly appeared to be the only existing deformity.

Comment on the technique. In the majority of the cases the contrast medium was injected through a heart catheter (nos. 8, 9 or 10 F); only in 3 cases was a cannula used. The contrast medium used was Diodrast or Umbradil, in a 70 per cent solution in 12 cases and a 50 per cent solution in 2 cases; 50—80 cc were injected. In patent ductus arteriosus, the circulating mass of blood in the aorta is increased as the result of the shunt mechanism. A rapid injection is therefore necessary in order to obtain satisfactory opacity of the aorta. This aim was realized by using a pressure apparatus allowing the medium to be injected within 4 seconds

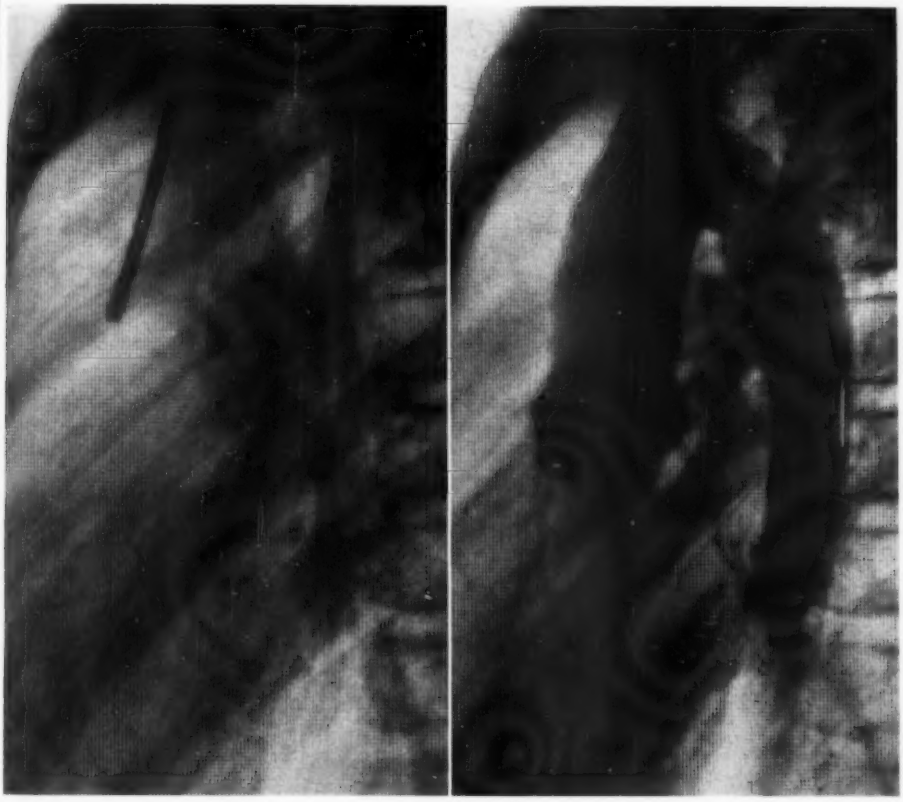

Fig. 4. Fig. 5.

Figs. 4 and 5. A girl, aged 11. Thoracic aortography. Contrast medium injected through a catheter. A small amount of contrast passed through the patent ductus. The opacity of the pulmonary artery is, however, clearly distinguishable when fig. 4 (picture taken before the injection) is compared with fig. 5 (picture taken during the injection).

or less. In the first few cases, however, the injection was done by hand and therefore took a much longer time (up to 10 seconds). The roentgenograms were taken at a rate of about 1 pair of plates (anteroposterior and lateral views) per second.

Results

The following features were observed in all cases:

1) *Contrast substance passed over from the aorta to the pulmonary artery.* The opacity of the pulmonary artery was clearly distinguishable

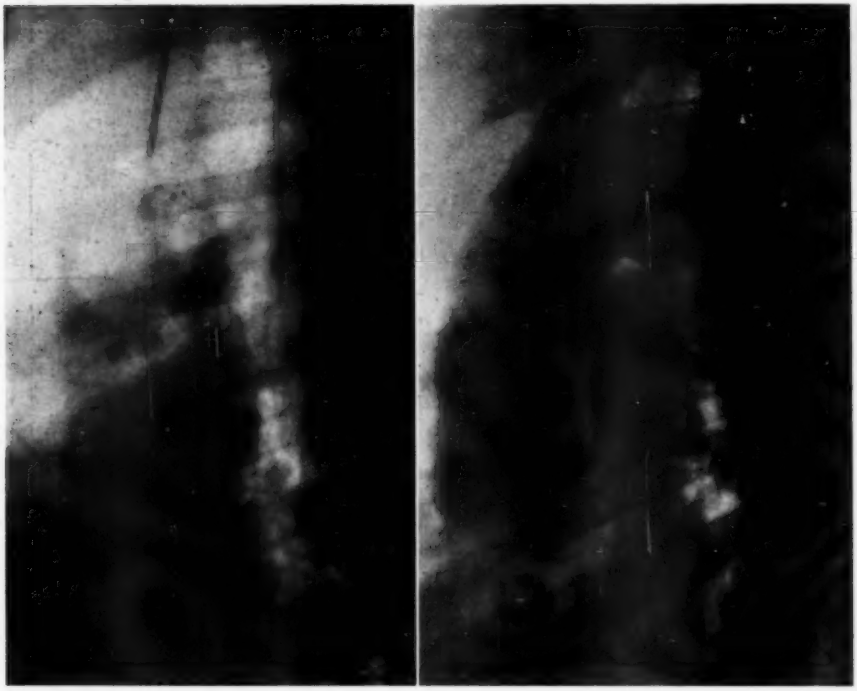

Fig. 6. Fig. 7.

Figs. 6 and 7. A woman, aged 39. Thoracic aortography. Contrast medium injected through a cannula. A large amount of contrast passed through the patent ductus. At the operation the diameter of the ductus was estimated to be 0.9 cm.

in all cases (figs. 2—9). In some cases the vessels of the left lung were more opaque than those of the right lung. This difference may conceivably have been due to the fact that the ductus did not lead to the main trunk of the pulmonary artery but instead to its left branch. However, in our material, the surgical notes do not contain any details as to the spot at which the ductus entered the pulmonary artery. In two cases where a careful blood gas analysis was carried out on blood samples from the two main branches of the pulmonary artery, the oxygen concentration was found to be considerably higher in the blood taken from the left branch. In these cases no distinct difference in opacity between the vessels of the right and the left lung was observed at the aortographic examination.

2) *The interarterial communication was a patent ductus arteriosus.*

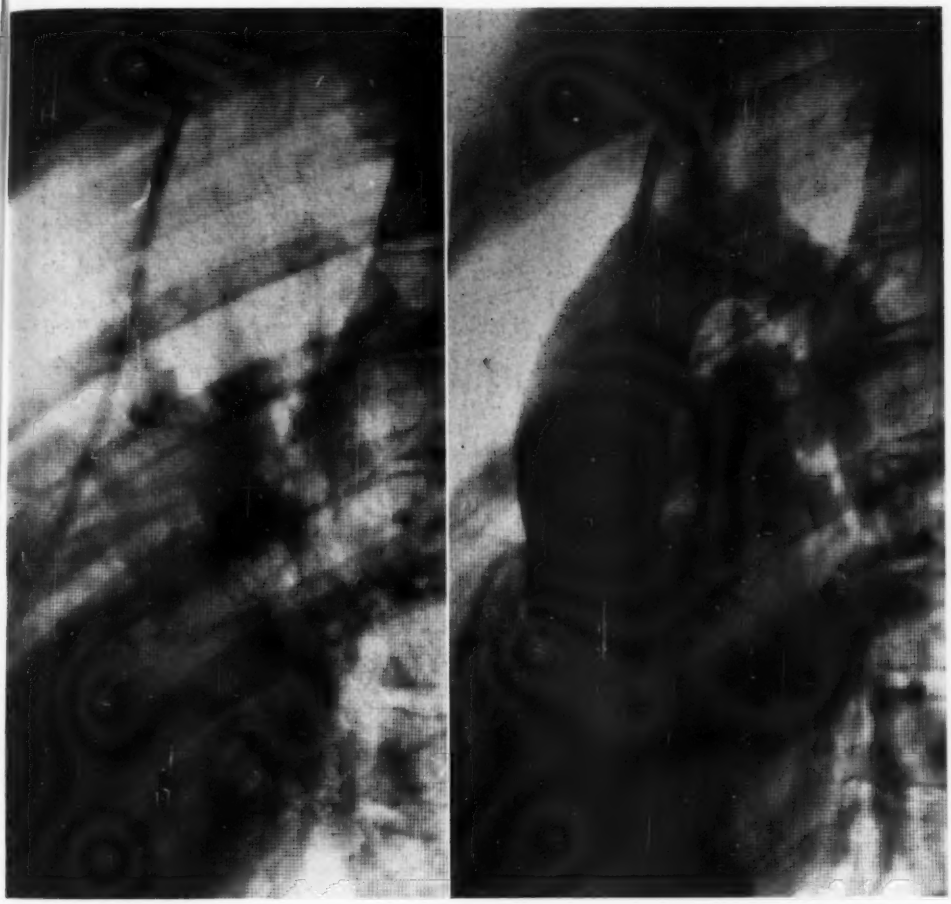

Fig. 8. Fig. 9.

Figs. 8 and 9. A woman, aged 22. Thoracic aortography. Contrast medium injected through a catheter. A small amount of contrast passed through the patent ductus to the pulmonary artery. Fig. 9 needs to be compared with fig. 8 (taken before the injection) in order to demonstrate the opacity of the pulmonary artery. At the operation the diameter of the ductus was estimated to be 0.5 cm.

The opacification of the pulmonary artery began when the contrast medium which had been injected into the aorta passed the site of the patent ductus. No other abnormal communication between the aorta and the pulmonary artery could be distinguished.

Fig. 10. A woman, aged 28. Thoracic aortography. Contrast medium injected through a catheter. The ductus is visualized (arrows). Case 6 in the table in fig. 12.

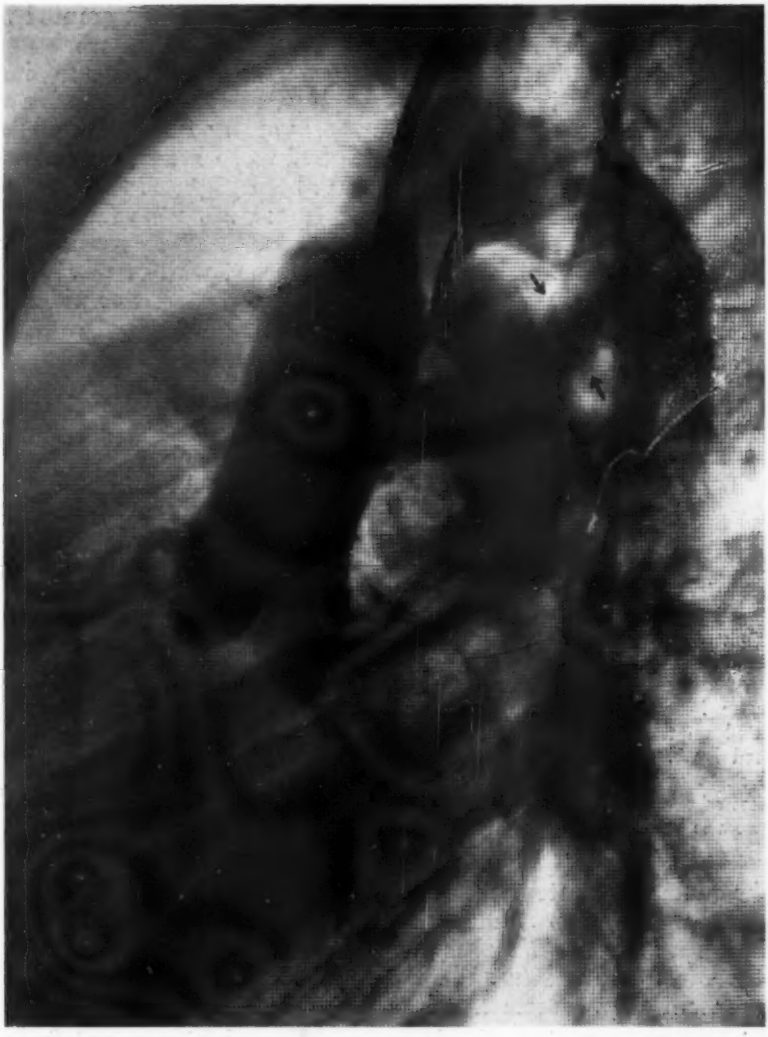

Fig. 11. A woman, aged 27. Thoracic aortography. Contrast medium injected through a catheter. The ductus is visualized. Case 4 in the table in fig. 12.

In 6 cases the ductus was so clearly opacified that its width could be estimated, and in 4 of these its length also was distinguishable (figs. 10, 11). It was *not possible* to make *exact* measurements of the width and length

of the ductus. When estimating the length we took it for granted that the ductus could not be shorter than the shortest distance between the aorta and the pulmonary artery and we thus obtained a minimum measurement. The estimation of the width was rendered difficult owing to the fact that branches of the pulmonary artery filled with contrast medium projected over the ductus. This had to be borne in mind when the width was being measured, and it has been given as the maximum measurement. The table shown in figure 12 compares the findings with respect to the length and width of the ductus obtained by aortography and at operation. The observations are in accord with one another, in that the ductus was found, at operation, not to be shorter or wider than had been calculated at the aortographic examination.

Case	Length (cm)		Width (cm)	
	Aortography	Operation	Aortography	Operation
1	0.5	0.5—0.6	1	0.7—0.8
2	0.5	0.6—0.7	1.2	1.0—1.1
3	—	0.3—0.4	2.5	1.9—2.0
4	0.5	0.6—0.7	1	0.6—0.7
5	—	0.3—0.5	1.5	0.9—1.0
6	1	0.8—1.0	1	0.7—0.8

Fig. 12. Comparison between measurements obtained for the length and width of the ductus with the aid of aortography, and at operation. — The values obtained by measurement from the roentgenograms have been reduced by 20 per cent to allow for the enlargement. The length is given in terms of the minimum measurement, and the width as the maximum figure. — The measurements obtained at operation refer to the outer length and outer diameter of the ductus. The inner measurements were calculated on the basis of these figures; the outer length measured at operation was increased by 0.2—0.3 cm, to allow for that part of the ductus situated in the walls of the aorta and the pulmonary artery; the outer diameter was decreased by the double thickness of the ductus wall, which was assumed to be 0.2 cm (a rough approximation, since the thickness of the ductus wall varies considerably from case to case).

The pulmonary artery was not opacified to an equal degree in all cases, and we began to wonder whether there might not be some *connection* between the *size of the shunt*, as estimated from the roentgenograms, and the *width of the ductus*. When the maximum density of contrast in the pulmonary artery seemed to be at least as great as in the aortic arch, in the anteroposterior view, we considered this to indicate a »large shunt». Judging the shunt in this way, we found a »large shunt» in 11 cases. In these cases the width of the ductus was found, at operation, to be 0.7 cm at the least, and 2.0 cm at the most. (Inner diameter calculated approximately.) In one case where the shunt was small the inner diameter of the ductus was calculated to be 0.5 cm. In the remaining two cases it was not possible to estimate the size of the shunt.

Fig. 13. A woman, aged 32. Thoracic aortography. Contrast medium injected through a catheter. Localized dilatation of the aorta beyond the ductus. A large shunt. At the operation the diameter of the ductus was estimated to be 1 cm.

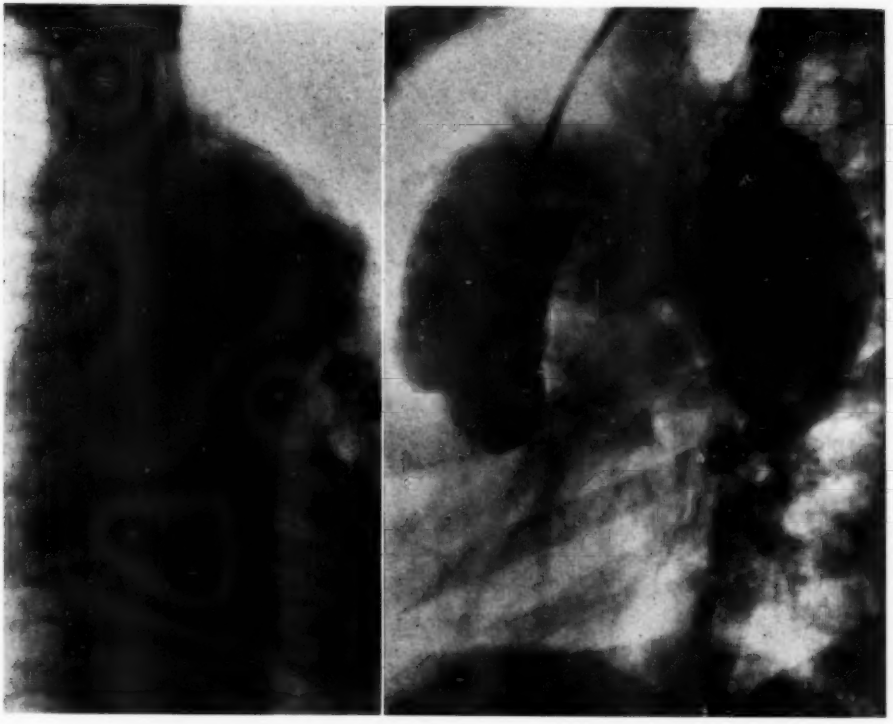

Fig. 14. Fig. 15.

Figs. 14 and 15. A woman, aged 23. Thoracic aortography. Contrast medium injected through a catheter. A large shunt. Pronounced localized dilatation of the aorta. At the operation the diameter of the ductus was estimated to be 1.2 cm.

These observations strengthened the fairly obvious supposition that a large shunt is not compatible with a very narrow ductus. The opposite condition, a small shunt through a wide ductus is, on the other hand, quite conceivable, and it has, as a matter of fact, been observed by the writers (in a child).

Localized dilatation of the aorta around the base of the ductus, such as has been observed by STEINBERG, GRISHMAN & SUSSMAN with the aid of angiocardiography (cf. p. 68), was clearly distinguishable in 7 cases and was suspected in a further 4 cases (fig. 13). In one case, this dilatation was of a high degree (figs. 14—15).

Children

Thoracic aortography has been carried out on *3 children* with a patent ductus arteriosus, aged 8, 11 and 12 years. All three cases have been verified by operation.

Comment on the technique. As has been mentioned before, rapid injection of the contrast medium is particularly desirable when thoracic aortography is to be performed in cases of patent ductus arteriosus. The rate of injection is dependent, among other things, on the diameter of the catheter (or cannula) that is used. It is often difficult, in children, to insert through a peripheral artery a catheter sufficiently large to allow a rapid injection. Therefore, when thoracic aortography is performed in children, an important condition for obtaining adequate opacity of the aorta is lacking. In one of the children we were able to insert a no. 8 F catheter (the same number as was used in the majority of the adult patients), in the other two a no. 6 F had to be used. In one case a 50 per cent solution was used, in the others a 70 per cent; 50 cc were injected in all three cases.

Results

In two of the children we observed the same features as were noted in all the adult patients, namely, that the contrast medium passed from the aorta to the pulmonary artery and that the interarterial communication was a patent ductus. In the third child — one of the cases where the contrast had been injected through a no. 6 F catheter — the aorta was so unsatisfactorily opacified that it was not possible to make any reliable observations. The patient had a very wide ductus. A blood gas analysis did not yield definite evidence of a shunt. In such a case, maximum opacity of the aorta would have been necessary to enable the patent ductus to be diagnosed by aortography. The case illustrates the limitations of thoracic aortography as a means of detecting patent ductus in children.

Discussion

The majority of the patients in our material had a typical, continuous murmur. The diagnosis of patent ductus arteriosus was therefore considered to be unmistakable, and it was confirmed with the aid of thoracic aortography. In three patients with an atypical murmur the diagnosis was not established until after a thoracic aortographic examination had been carried out. Admittedly, in these three cases, a blood gas analysis disclosed a higher oxygen concentration in the pul-

monary artery than in the right ventricle, and thus demonstrated that there was an interarterial communication between the aorta and the pulmonary artery, but the analysis naturally was incapable of revealing the exact site of the interarterial pathway.

One of the cases where there was a typical murmur is of particular interest. A carefully performed blood gas analysis failed to yield unequivocal evidence of an interarterial shunt, but when a thoracic aortographic examination was carried out contrast medium was plainly seen to be passing from the aorta to the pulmonary artery through a patent ductus (figs. 8—9).

Can thoracic aortography furnish, in addition to the diagnosis, sufficiently valuable information to justify its use, even when the clinical diagnosis of patent ductus arteriosus is definitely established? In the majority of our cases we were able to estimate the width of the ductus, either indirectly by means of observation of the size of the shunt (in the patients with a wide ductus), or by making direct measurements of the contrast-filled ductus. It was also possible, in some cases, to estimate the length of the ductus. Anatomical details of this kind are not without significance when the surgical intervention is being planned. A very short and wide ductus cannot be ligated but must, instead, be divided and sutured. It is for the surgeon to decide how detailed he requires the anatomical information to be. There is no absolute indication for thoracic aortography in clinically established cases of patent ductus arteriosus.

Conclusions

1) *Thoracic aortography is necessary to ensure a sure diagnosis in cases of patent ductus arteriosus with an atypical murmur.*

2) *Thoracic aortography furnishes, besides the diagnosis of patent ductus, valuable information regarding the anatomy.*

SUMMARY

Thoracic aortography has been carried out in 14 adults and 3 children with patent ductus arteriosus. In 3 cases where there was an atypical murmur the diagnosis could only be established with the aid of aortography. In the majority of the cases, thoracic aortography furnished, in addition to a sure diagnosis, valuable information regarding anatomical details.

ZUSAMMENFASSUNG

Aortographie der Brustaorta wurde an 14 Erwachsenen und 3 Kindern mit offenstehendem Ductus arteriosus Botalli vorgenommen. Bei 3 Fällen mit atypischem Nebengeräusch konnte die Diagnose nur mit Hilfe der Aortographie gestellt werden. Bei der Mehrzahl der Fälle gab die Aortographie der Brustaorta nicht nur eine sichere Diagnose sondern auch wertvolle Auskünfte über anatomische Einzelheiten.

RÉSUMÉ

L'aortographie thoracique a été exécutée chez 14 adultes et 3 enfants atteints de persistance du canal artériel. Dans trois cas où existait un souffle atypique le diagnostic ne put être posé que grâce à l'aortographie. Dans la majorité des cas ce mode d'exploration, en plus de la certitude diagnostique, a fourni des renseignements précieux touchant des détails anatomiques.

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FROM THE DERMATOLOGY DEPARTMENT OF THE FINSEN INSTITUTE, COPENHAGEN, DENMARK (HEAD: PROFESSOR SVEND LOMHOLT, M. D. †) AND THE BIOPHYSICAL LABORATORY OF THE UNIVERSITY OF COPENHAGEN (DIRECTOR: PROFESSOR H. M. HANSEN, PH. D.)

SPECTRAL INVESTIGATIONS OF CARBON ELECTRODES FOR LIGHT THERAPY[1]

by

B. Buchmann-Olsen and *K. G. Hansen*

Before and during the war the Finsen Institute chiefly used therapeutic carbons from Siemens, particularly Siemens A (pure carbon) and Siemens Schneeweiss (impregnated carbon) for light therapy. The former type was preferably used for the treatment of patients with diseases of the respiratory system, while for other purposes Schneeweiss carbons were used. The advantage obtained by using Schneeweiss carbons is caused by the well-known fact that the radiation from this type of carbon contains more ultraviolet radiation than that of pure carbon. On the other hand the impregnated carbons will, while burning, give off »metal vapour» (oxides), which may cause the air in the room used for the treatment to have an irritating effect on the patient's respiratory organs. By means of suitable (draughtfree) ventilation this drawback was remedied, and impregnated carbon was usually preferred for light therapy.

Towards the end of the war the Siemens carbons disappeared from the market, and the Finsen Institute had to change over to other types of carbon of which the institute had no experiences neither as regards physical nor clinical properties. A closer investigation of the carbons which were now imported, was thus indicated, and the present investigation comprises the results of examinations of 13 types of electrodes. The results are published because many therapeutists — as it appears from enquiries directed to the Finsen Institute — are interested in this matter.

Without otherwise discussing the biological effect of the different spectral regions, we have compared the different types of carbon by measuring the spectral energy emitted within the wavelength range 500

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mμ to 300 mμ. We have further measured the rate at which the carbon is consumed, expressed as the number of millimeters by which the length of the carbon electrodes are shortened per hour, and the amount of ashes in milligram per hour. In order to obtain a further characterisation of the carbon types we have described the stability of the arc and the tendency of the ashes to burn through filter paper (corresponding to a sheet) placed at a distance of 30 cm below the arc lamp.

The distribution of spectral energy was determined by means of a measuring technique, which is described in detail in a paper published by one of the authors of the present work (HANSEN (1)). The radiation is spectrally resolved by means of a double monochromator, and the measurement of the radiation is performed by a selenium barrier-layer photocell. The carbons were placed in a Finsen Universal lamp which was suspended in such a way that the location of the arc was well defined in relation to the monochromator and photocell. The arc is fed with alternating current from a stray field transformer in the same way as the usual Finsen lamps, and for each carbon type we have used a tapping from the transformer, in other words burning conditions, which produce the most stable arcs of suitable length, about 2 cm. Consequently the electrical data vary somewhat from carbon type to carbon type, but not more than to ensure that the relative spectral curves are comparable.

An image of the arc is thrown onto the collimator mirror of the monochromator (fig. 1) by means of an inclined plane mirror P and a

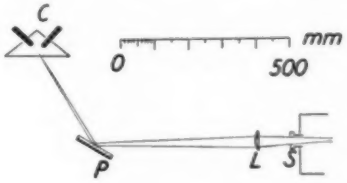

Fig. 1.

quartz lens L. By this arrangement we employ a cone of rays with an apical angle of about 5° out of the radiation from the arc, the cone of rays forming an angle of about 45° with the normal, which corresponds approximately to the direction of the light towards a patient according to the usual arrangement for light therapy. The mirror P is coated on its front with aluminium, *i. e.* within the spectral range examined the mirror may be considered to produce a non-selective reflection (conf. LUCKIESH (2)). The photocell is a selenium barrier-layer photocell (manufacture EEL) without surface coating with known spectral sensitivity.

The arc lamp was automatic, but on account of inhomogeneity of the carbons, circulation of the air, etc. the electrical data of the arc and consequently its radiation varied considerably. In each experimental

series the radiant flux, expressed by the deflection u of the galvanometer, has been determined at the same voltage, which in practice means at very much the same electric power.

The measuring technique was as follows: The monochromator was set at a certain wavelength λ, and the galvanometer deflection u obtained for the desired value of the voltage was read. The mean value u_m of three readings was taken and the spectral energy E_λ corresponding to the wavelength λ was calculated from the formula:

$$E_\lambda = u_m/(V_\lambda D_\lambda),$$

where V_λ is the spectral sensitivity of the selenium photocell and D_λ is the dispersion of the monochromator which is dependent on the wavelength. E_λ is thus a relative value, dependent on the measuring apparatus applied, but as all the examinations of carbons described here have been made with the same set-up and as moreover the electric data of the various arcs do not differ much, the values of E_λ within the same spectrum as well as within different spectra are quite comparable.

The error of E_λ is chiefly conditioned by the fluctuations in the electric data of the arc, the result of which is that the error of u_m is 4—5 %. The values of V_λ and D_λ are both subject to an error of about 1 %, so that the error to which E_λ is subject is about 7 %.

The following carbon electrodes were examined:

1.	National Carbon B.	American carbons
2.	National Carbon C.	
3.	National Carbon Sunshine	
4.	Lorraine Heliocure 802	French carbons
5.	Lorraine Heliocure 802—01	
6.	Lorraine Heliocure 810	
7.	Pool Carbon, White Flame (Ship)	British carbons
8.	Ship Sunlight	
9.	Morganite TCC	
10.	Morganite TCE	
11.	General Electric, Sunnich	
12.	Siemens A	German carbons
13.	Siemens Flame Carbon 301 (Schneeweiss)	

The Siemens carbons have been included in the investigation to establish a comparison between these well-known and previously extensively used carbon electrodes.

Figures 2—12 illustrate the distribution of spectral energy for the different carbons. It is seen from the figures that according to the distribution of spectral energy the carbons may be classified in two groups,

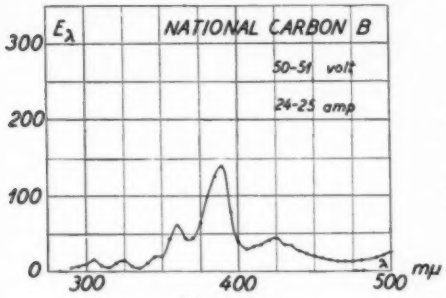

Fig. 2.

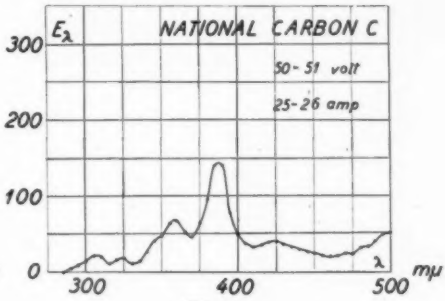

Fig. 3.

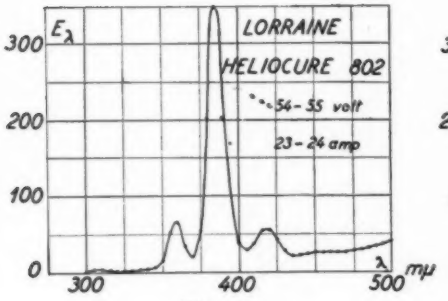

Fig. 4.

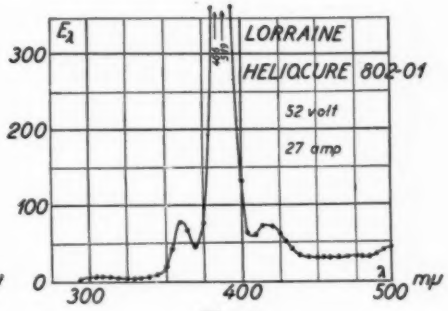

Fig. 5.

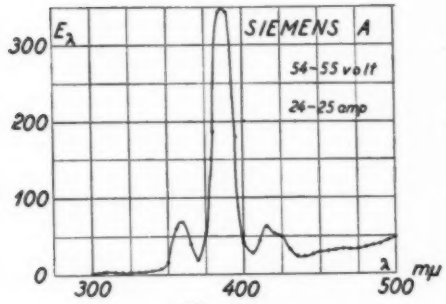

Fig. 6.

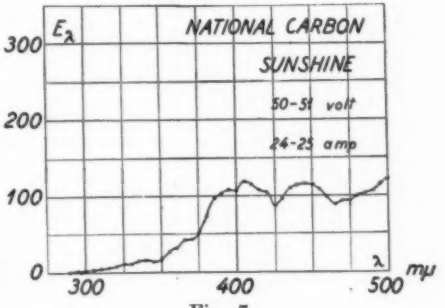

Fig. 7.

one corresponding to Siemens A and another corresponding to Siemens Schneeweiss.

In the first group we have National Carbon B and C, Lorraine Heliocure 802 and 802—01, Morganite TCC and, of course, Siemens A. For these carbons the spectral energy distribution is very much the same. The energy

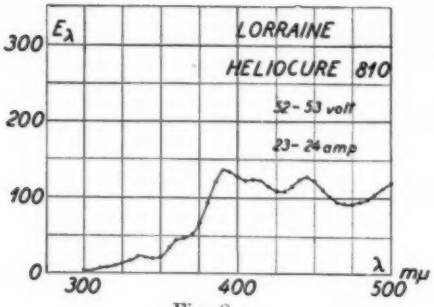

Fig. 8.

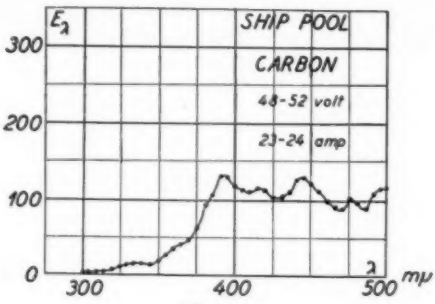

Fig. 9.

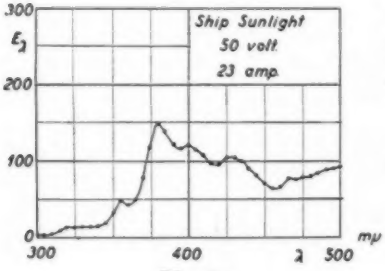

Fig. 10.

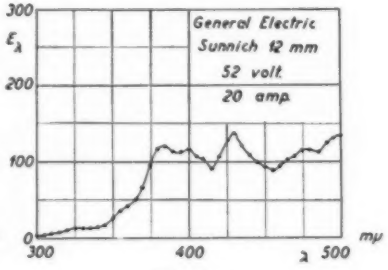

Fig. 11.

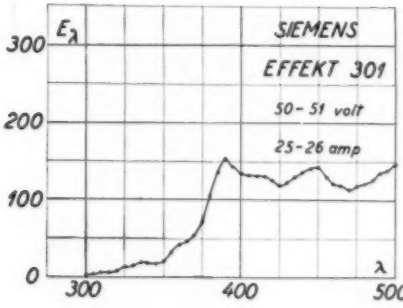

Fig. 12.

radiated from National Carbon B and C is, however, somewhat lower, perhaps because these carbons are intended to burn at a higher amperage; it can be seen that National Carbon B and C are impregnated carbons and not pure carbons, because the spectral energy in the range 300—350 mμ is somewhat larger than in case of pure carbons. The arc produced by Morganite TCC carbons is so instable that the spectral energy distribution cannot be determined with an accuracy corresponding to the

above. The other characteristics of the different carbons will appear from the table.

The other group comprises National Carbon Sunshine, Lorraine Heliocure 810, Ship Pool Carbon, Ship Sunlight, Morganite TCE, General Electric (Sunnich) and Siemens Schneeweiss. The spectral energy distribution is fairly monotonous, the energy being almost constant in the visible part of the spectrum, the cyanogen band at 388 mμ almost completely suppressed, and the curve sloping smoothly downwards through the ultraviolet range. The spectral curve of Morganite TCE carbons has not been reproduced as this arc was also too instable.

In summing up we may say that a perfectly satisfactory carbon arc for therapeutical purposes is obtained by using — in the case of pure carbon — Heliocure 802—01 and — in the case of impregnated carbon — Heliocure 810 or General Electric Sunnich. Among the characteristics of the other types of carbons it may be noticed that Morganite TCC does not produce measurable quantities of ashes, but that the stability of the arc is very low, and that Ship Sunlight Carbon produces a stable arc, but a considerable amount of ashes and tendency to burn through the paper.

The curves reproduced may, with a certain approximation, be used as a basis for comparison with the Siemens carbons for the purpose of determining the dosage.

Table

Designation	Type	Stability of arc.	Consumption mm/hour	Ashes mg/hour	Extent to which filter paper is burned through
National Carbon B	Impregnated	Fairly stable	35	50	Some
National Carbon C	Impregnated	Fairly stable	34	334	Considerable
National Carbon Sunshine	Impregnated	Instable	45	506	Extreme
Lorraine Heliocure 802	Pure	Stable	35	26	None
Lorraine Heliocure 802—01	Pure	Extremely stable	34	11	None
Lorraine Heliocure 810	Impregnated	Extremely stable	29	203	Traces
Pool Carbon White Flame	Impregnated	Fairly stable	34	324	Considerable
Ship Sunlight	Impregnated	Stable	28	133	Considerable
Morganite TCC	Pure	Extremely instable	42	0	—
Morganite TCE	Impregnated	Extremely instable	29	285	—
General Electric Sunnich	Impregnated	Stable	38	44	Some
Siemens A	Pure	Stable	37	14	None
Siemens Schneeweiss	Impregnated	Fairly stable	48	70	None

SUMMARY

A number of carbon electrodes for therapeutical purposes have been examined. The spectral distribution of energy, the stability of the arc, the speed at which the electrodes are consumed, as well as the amount of ashes produced have been determined, and the extent to which filter paper (representing a sheet) is burned through has been examined.

From a spectral point of view carbon electrodes may be classified in two groups: pure carbon electrodes and impregnated carbon electrodes, and within these groups there is no fundamental difference between the various makes. Differences only manifest themselves with regard to the stability of the arc and the other characteristics examined.

ZUSAMMENFASSUNG

Eine Anzahl Kohlen-Elektroden für therapeutische Zwecke sind untersucht worden. Die spektrale Effektverteilung, die Stabilität des Bogens, die Geschwindigkeit, in welcher die Elektroden verbraucht werden, sowie die Aschenmenge sind konstatiert worden, und der Umfang in welchem ein Filtrierpapier (in Stelle eines Lakens) durchgebrannt wird, ist untersucht worden.

Vom Spektral-Gesichtspunkt aus können Kohlen-Elektroden in zwei Gruppen klassifiziert werden: Rein-Kohlen-Elektroden und »Effekt»-Kohlen-Elektroden, und innerhalb dieser Gruppen gibt es keine wesentlichen Unterschiede zwischen den verschiedenen Fabrikaten. Unterschiede offenbaren sich nur mit Bezug auf die Stabilität des Bogens und die anderen Charakteristiken, welche untersucht sind.

RÉSUMÉ

Une quantité d'électrodes de charbon pour usages thérapeutiques de différentes marques a été étudiée. Ont été étudiés: la répartition de l'effet spectral, la stabilité de l'arc, la rapidité de combustion des électrodes, la quantité de cendre qu'ils laissent et dans quelle mesure un papier filtre (mis à la place d'un drap) est brulé.

Au point de vue spectral les électrodes de charbon divisés en deux groupes, électrodes de charbon pur et électrodes de charbon »à effet», ne démontrent pas de différences notables entre les produits des diverses marques. Elles apparaissent uniquement par rapport à la stabilité de l'arc et des autres points étudiés.

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FROM THE MUNICIPAL HOSPITAL ROENTGEN DEPARTMENT, UNIVERSITY OF AARHUS, DENMARK (CHIEF: PROFESSOR CARL KREBS)

CALCIFICATION OF THE VASA DEFERENTIA[1]

by

Poul E. Andersen

Calcification of the seminal vesicles, ampullae and vasa deferentia is a very rare condition and has been dealt with only a few times in the radiological literature. It is so rare that our case with its extensive calcifications seems worthy to report.

The earliest pathological reports of calcification of the seminal vesicles and vasa deferentia are apparently those by CLEMENT (1830) and LALLEMAND (1836) on calcification of both seminal vesicles, by DUPLAY (1855) on calcification of both ampullae and by GUELLIOT (1883) on calcification of both vasa deferentia and seminal vesicles.

The first roentgenologically demonstrated cases were those reported by KRETSCHMER (1922), showing calcification of a left seminal vesicle, and BIANCHINI (1930), who reported calcification of the entire left and right vasa deferentia and both ampullae. Later HOFER & LOSSEN (1932) reported a case with calcification of both ampullae and passing of a small stone from the left vas deferens. Comprehensive articles on the subject have been published by JANKER (1935), MARKS & HAM (1942) and LOWSLEY & RIABOFF (1942).

As regards the etiology KRETSCHMER divided cases of calcification of the deferential ducts and seminal vesicles into two groups: 1) senile calcification occurring in men of advanced years, and 2) calcification due to tuberculosis. A similar division has been made by other authors, and a grouping of the cases in 1) inflammatory and 2) non-inflammatory has as regards the experiences of later authors proved justified, especially as the calcification of the seminal vesicles and the calcification of the vasa deferentia — at least to a rather large extent — appear to be of different etiology and occurrence. The calcification of the seminal vesicles is usually found in patients with tuberculosis (FRAENKEL,

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GEORGE, JANKER, KRETSCHMER) or other chronic inflammatory conditions, especially gonorrhea (COTTENOT & BINET DU JASSONEIX, GRASHEY, HEITZMANN, JANKER, KRETSCHMER), while calcification of the vasa deferentia is met with especially in elderly men suffering from extensive arterial calcification (SCHELLENBERG) and above all in diabetics (MARKS & HAM).

At present a total of 25 cases of calcification of the vasa deferentia has been reported, but it is the belief of the author — although JANKER was able to find only 2 cases among 1,000 pyelographies — that this figure does not represent the true incidence of the condition.

Segmental calcification of the vasa deferentia might easily be overlooked, overshadowed at barium enemas and pyelo-cystographies or misinterpreted on conventional films of the pelvis unless the calcified segment should happen to be extrapelvic or in the region of the ampulla where the course of the ducts is unlike that of any vessel normally occurring in the male pelvis. If the film happens to include the scrotum and if the calcification is in the extrapelvic and scrotal segment of the vas deferens the diagnosis is obvious, since the vas has a rather smooth course and its lumen is greater than that of the arteries accompanying the funicle.

Calcification of the vas deferens, especially the ampullar segment, associated with calcification of the seminal vesicles has been reported a few times (CHIARI, MARKS & HAM), but these cases appear to be calcifications occurring in chronic inflammatory, tuberculous or gonorrhoic conditions of the seminal vesicles spreading through the ampulla into the portion of the vas deferens lying medial to the ureters, and it is the impression of the author that calcification of the vasa deferentia and of the seminal vesicles are two quite different conditions, a view which also seems justified remembering that the two structures serve different functions and that the seminal vesicles are more frequently the seat of chronic infection.

Calcification throughout the whole course of both ducts has only been reported by BIANCHINI and MARKS & HAM. Thus the author's case is the third known case. Usually the calcification is most dense in the intrapelvic portions of the ducts and only present in lesser amounts in the segment in the inguinal canal, but a case has been reported by MARKS & HAM showing only calcification of the extra-abdominal portion of the ducts.

Etiology and Pathology

While only 4 of the reported 25 cases of calcification of the vasa deferentia appear to be the result of tuberculosis, gonorrhea or other

chronic inflammatory disease of specific or non-specific nature, the remaining 21 cases are presumably on the basis of degenerative processes of the muscularis since they occurred in elderly men, the average age being about 60 years contrasting c. 32 years in the cases caused by chronic infections.

While no history of diabetes was found in the cases reported before 1942, MARKS & HAM reported the finding of diabetes in 6 of their 9 cases with an average duration of the diabetic condition of c. 14 years. The author's case was also in a diabetic. In at least 5 of the 9 patients reported by MARKS & HAM and in the author's case the process was associated with extensive arterial calcification. In several cases the degree of arterial calcification was even greater than that usually seen in diabetes. Since none of these patients gave any definite history of infection of the genital tract, one has been led to associate the process of calcification in the vasa deferentia with the diabetes and the degenerative process in the arteries. The cause why diabetes has not been acknowledged as being of etiologic importance until the latest years, is probably that the Insulin therapy has given patients suffering from diabetes a longer life so that a greater percentage of these patients now will reach the period of degenerative vascular diseases. In the future calcifications of the vasa deferentia and vesicles must be expected to be seen in diabetics with increasing frequency.

Only in a few cases microscopic examination has been performed (CHIARI, DUPLAY, FRAENKEL, MARKS & HAM). In these cases the calcification was found in sclerotic or hyaline degenerated connective tissue within the muscular wall of the duct; in no case signs of inflammatory processes were reported.

Diagnosis and Differential Diagnosis

No symptoms are ascribed specifically to this condition, but when a small stone is present in the lumen of the vas deferens it may manifest itself by an attack of spermatic-colic pain and blood in the urine (HOFER & LOSSEN). Usually, however, the condition is quite without symptoms and the diagnosis of calcification of the vas deferens has to be based upon the roentgenologic findings, which is as a rule occasional, and may be confirmed by vasography (LOWSLEY & RIABOFF).

In case of calcification of scrotal segments of the ducts the diagnosis should be easy as the vas deferens has a relatively smooth course and its lumen is greater than that of the arteries of that region.

When calcification is present only in a segment of the intrapelvic or inguinal portion — as was the case in some of the patients reported by MARKS & HAM — the diagnosis may be suspected when double

parallel lines of calcium density are seen to cross the obturator foramen obliquely, downwards and medially. Linear shadows in this region should always make one suspect calcified vasa deferentia but it must be remembered that the shadows cast by a calcified internal pudendal artery pursue the same course for some distance and so may be the cause of misinterpretation. In case of extensive arterial calcification one may note the origination of the internal pudendal artery from the internal iliac artery in the lateral portion of the pelvis and its course after crossing the obturator foramen medially to supply the tissues about the anus and the root of the penis.

The course of the vas deferens as a whole within the pelvis is unlike that of any artery normally occurring in the male. MARKS & HAM noted that in each case in which the intrapelvic portion of the vas deferens was calcified, the point at which it arched over the ureter was clearly shown by an accentuation of the shadow. This arching of the duct over the ureter is a prominent feature in its course along the posterior and lateral walls of the pelvis and is clearly shown in all anatomical texts.

Case report

A 62-year-old teacher was admitted to the Medical Department of the Municipal Hospital, University of Aarhus, on Nov. 29, 1949. He gave a history of diabetes which had been diagnosed 13 years ago and only poorly treated, but no history of tuberculosis or venereal disease was obtained, and the Wassermann-Kahn-Meinicke tests for syphilis were negative twice. For $1^1/_2$ months he had had abdominal colics at irregular intervals, constipation followed by diarrhea, rectal tenesmi, dull pain in the lumbar and sacral regions and a few times fresh blood and mucus in the stools. The general condition was good, but the liver was felt about 2 inches below the costal margin and there was some ascites.

Rectal examination revealed a submucous firm prominence at the site of the seminal vesicles, but rectoscopy did not show any tumour and a biopsy was negative. The sedimentation rate was about 80 mm, and the Meulengracht icterus index was 11.

While the chest film, examination of the ventricle and the small intestines did not reveal anything of interest, the barium enema showed a carcinoma of the sigmoid which accounted for the rectal symptoms, the enlargement of the liver and the elevation of the sedimentation rate.

On the films of the pelvis a most peculiar calcification was seen (fig. 1 & 2) on each side of the mid-line, almost the shape of the horns

Fig. 1 showing the course of the calcified vasa deferentia across the foramina obturatoria and down into the scrotum.

Fig. 2 showing the ampullar portions of the vasa deferentia more clearly and the calcified vesicles.

of a buffalo or yak, pointing upwards laterally and continued by a parallelly double-lined and 2—3 mm broad calcification running a semicircular course laterally downward and medially across the obturator foramen and from there down into the scrotum, symmetrically on both sides. Just below the calcified ampullae were some more irregular calcifications presumably localized in the seminal vesicles or perhaps the prostate. The calcifications were so extensive that no other diagnosis than calcified vasa deferentia could be made. Marked calcifications of the arteries of the pelvis were also noticed.

Thus this is a case of calcification of the vasa deferentia in an elderly man suffering from diabetes and arteriosclerosis but without signs of tuberculosis or chronic venereal disease and thus quite in conformity with the majority of cases reported by MARKS & HAM and supporting the theory of the etiologic importance of diabetes in this condition.

SUMMARY

A case of extensive bilateral calcification of the vasa deferentia is presented, the third to be reported in the literature. The author emphasizes the association between calcification of the seminal vesicles and chronic inflammatory conditions as tuberculosis and gonorrhea and between calcification of the vasa deferentia and diabetes. Also the patient reported had a history of diabetes of long duration as the majority of the cases reported during the last decennium. Radiographs are presented showing the very extensive calcifications which made the diagnosis obvious.

ZUSAMMENFASSUNG

Ein Fall — der dritte in der Fachliteratur — von ausgedehnter Verkalkung der Vasa deferentia wird mitgeteilt. Der Verfasser hebt die Verbindung zwischen Verkalkung der Vesiculae seminales und chronischen, inflammatorischen, tuberkulösen oder gonorrhoischen Zuständen und zwischen Verkalkung der Vasa deferentia und Diabetes hervor. Auch der Patient, der mitgeteilt wird, hatte seit 13 Jahren Diabetes, gleich wie die meisten Patienten, die in der Literatur des letzten Decennium mitgeteilt sind. Röntgen-aufnahmen zeigen die sehr ausgedehnten Verkalkungen, welche die Diagnose ganz einfach machten.

RÉSUMÉ

L'auteur rapporte un cas de calcification extensive des canaux déférents, le troisième dans la littérature radiologique. L'association entre la calcification des vésicules séminales et les conditions inflammatoires chroniques, tuberculeuses ou vénériennes, et ça entre la calcification des canaux déférents et le diabète sont accentuées. Le malade, dont l'auteur rapporte, avait aussi le diabète de longue durée comme la plupart de cas rapportés pendant la décade dernière. Les radiographies, qui ont fait le diagnose certain, sont présentées, montrantes les calcifications très extensives.

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A CASE OF PYELO-URETERITIS CYSTICA, DIAGNOSED BY PYELOGRAPHY[1]

by

J. R. von Ronnen and *H. Dormaar*

Though the diagnosis pyelo-ureteritis cystica has been made several times in the last decennaries by means of intravenous or instrumental pyelography, the picture yet remains so remarkable that publication of another case seems to be quite justified. The more as most publications display very beautiful drawings of the macroscopic preparation, if the kidney was removed, or micro-photos of the changes of the cystic mucous membrane, but strangely enough, show only a few or not very clear roentgen pictures. Following our case, in which we according to our opinion justly diagnosed pyelo-ureteritis cystica, we hope to demonstrate clearly the several aspects of the roentgen picture. About the etiology, pathogenesis and microscopic anatomy of this disease such excellent articles have already been published (BOTHE and CRISTOL; BIEBERBACH, COOK and GOODALE) that it is unnecessary to go into this matter extensively.

Therefore we will restrict us to some short remarks. It is generally admitted that the cystic changes in the mucosa of pyelum, ureter or bladder occur under influence of a chronic low-grade infection. The pathogenesis is explained in the most acceptable way by the hypothesis of VON BRUNN (1893: downward proliferation of epithelial sprouts and forming of epithelial nests when their stalks to the surface epithelium become severed; degeneration of the centers of the nests result in cyst formation). Macroscopic and microscopic cysts are found, ranging from some fractions of a mm. to several cm's in diameter; the form is round or oval. The cysts are situated beneath as well as above the level of the mucous membrane. The macroscopic cysts which protrude above the

[1] Submitted for publication, April 12, 1950.

level of the mucosa are responsible for the changes in the roentgenogram, which make it possible to diagnose pyelo-ureteritis cystica.

Our patient, the 35 years old Javanese soldier K., was admitted to the Army hospital in October 1949 because since a week he complained of slight pain in the left side and had noticed that the urine had a reddish colour some times.

At admission patient seemed to be in a good general condition and he did not make an ill impression. Physical examination displayed, except tenderness on pressure and percussion in the left kidney region, no abnormalities. The history was not clear and revealed nothing important. Urine examination: normal chemical findings, the sediment contained some leucocytes and erythrocytes. After some days of bedrest the tenderness in the left side decreased as well as the urine abnormalities. After that the patient was sent to us for an intravenous pyelography.

On the plain roentgenogram, made before the injection of Pyelosil was given, we detected no abnormalities.

The roentgenograms made after the injection of the contrast medium show a normal secretion of the drug. At the right side the shape of the renal pelvis and ureter is normal and the shadow of the filling is homogeneous. At the left side there are distinct abnormalities:

a) the renal pelvis is smaller than at the right side;

b) the outline of the pelvis and uretero-pelvic junction as well as the pyelographic shadow show small round and oval filling-defects (fig. 1);

c) in the pyelographic shadow is a mucosal pattern visible not unlike mucosal rugae of the stomach (fig. 1);

in a later phase the filling of the renal pelvis is less and the »rugae» are a bit more pronounced (fig. 2).

The calices are remarkably slender and the fornices are sharp. Instrumental pyelography followed on our request. The result was:

a) after the filling of the renal pelvis with the contrast medium the pyelographic shadow has the same appearance as was seen with the intravenous method (fig. 3);

b) after some time, when the pelvis had almost emptied itself, we filled this with oxygen with the idea to make still clearer visible the changes of the mucous membrane by means of double contrast. We did this in analogy to the double contrast method as it is known in the examination of the bladder.

The picture we obtained now is extraordinary illustrative and has the resemblance of a membrane covered up with sago-grains: the whole renal pelvis and the first part of the ureter is strewed with small round translucent spots, surrounded by diluted contrast medium (fig. 4).

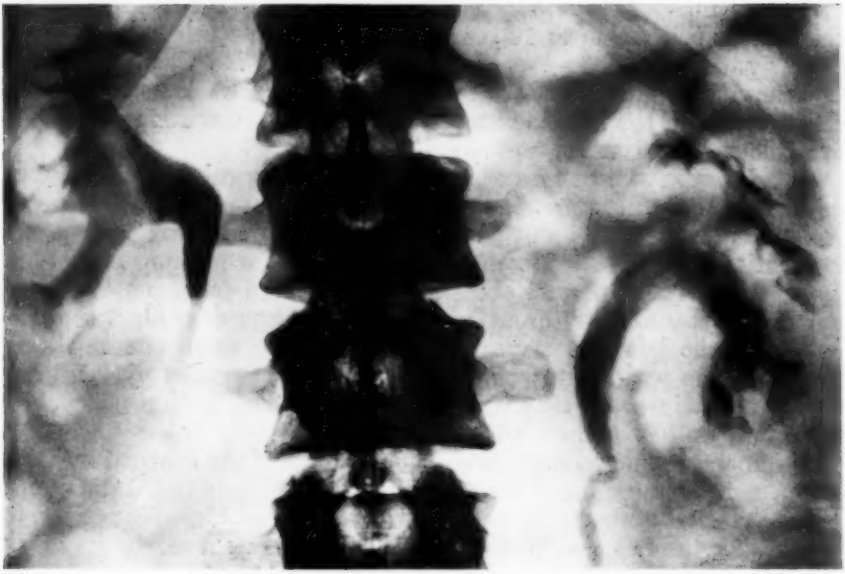

Fig. 1. Urography. Small round and oval filling defects in the left pelvis.

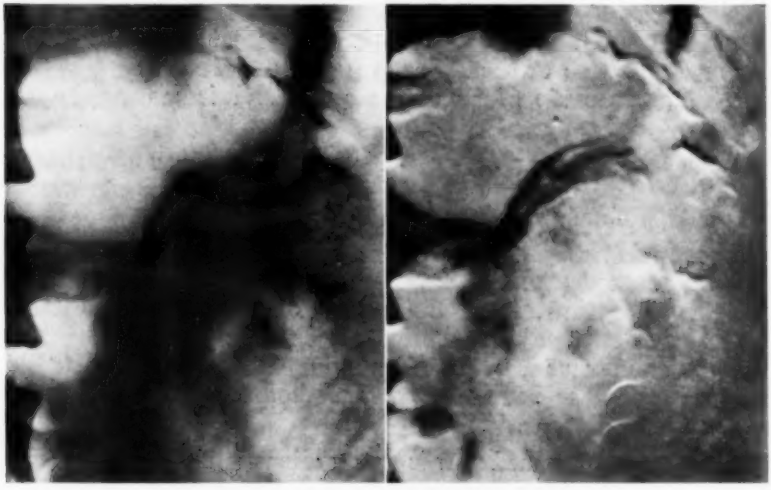

Fig. 2 a. Fig. 2 b.

Fig. 2. Urography. Less contrast in the left pelvis than in fig. 1. A mucosal pattern like the mucosal rugae of the stomach is visible.

Fig. 3 a. Fig. 3 b.

Fig. 3. The pyelographic examination gives the same picture as the urography.

Fig. 4. The pelvis is distended with oxygen when still a small amount of positive contrast is left. The mucous membrane is covered with small round cysts. (Double contrast method.)

The »rugae» are no more to be seen, possibly by cause of the stronger drawing-out, by the filling, of the walls of the renal pelvis.

So we have to suppose, according to the roentgen pictures, that the left pyelum and first part of the ureter are covered with numerous elevations of the size of a sago-grain.

The discongruence between the picture of the »rugae» and the picture of the sago-grains we tried to explain by considering the possibility that the »rugae» are caused by conglomerates of elevations separated by chiefly longitudinal furrows of more or less normal mucosa.

The diagnosis pyelo-ureteritis cystica has become very probable by this. The differential diagnosis concerns blood-coagula, small uric acid calculi, airbubbles, papillomata. Accurate examination of the roentgen pictures we got must exclude these possibilities and there remains as diagnosis the pyelo-ureteritis cystica.

In the literature are mentioned as roentgen symptoms, to be found with pyelo-ureteritis cystica, beside the translucent spots in the pyelographic shadow, a dilatation of the ends of the major calyces with narrowing of the arms of the calyx below and cystic dilatation of the ureteropelvic junction (not a true pyelectasis). HINMAN, JOHNSON and MCCORKLE described these last symptoms for the first time and stated that these symptoms are typical of pyelitis cystica. In our case, however, they are missing. We suppose that these symptoms will be caused by a large number of cysts and/or cysts of a large size, so that partial closing occurs of the fairly narrow parts (calyces majores, ureteropelvic junction) resulting in stagnation and, as consequence, dilatation of the behind situated parts. So in our case the missing of these symptoms may be caused by the small size of the cysts by which the cysts give no rise to obstruction.

SUMMARY

Description of a, by radiological methods diagnosed, case of pyelo-ureteritis cystica. Attention is drawn to the roentgen picture of this disease and especially to the illustrative picture obtained with the double-contrast method.

ZUSAMMENFASSUNG

Beschreibung eines Falles von Pyelo-ureteritis cystica, wo die Diagnose röntgenologisch gestellt wurde. Nachdruck wird gelegt auf das röntgenologische Bild dieser Krankheit und speziell auf das schöne Bild, das mit der Doppeltkontrastmethode erzielt wird.

RÉSUMÉ

Description d'un cas de pyelo-ureteritis cystica dont la diagnose était posée radiographiquement. L'attention est attirée sur les signes radiologiques et spécialement sur l'image caractéristique qu'on obtient avec la méthode du contraste double.

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AUS DEM SERVICE DE RADIOLOGIE ET D'ÉLECTROTHÉRAPIE DE L'HÔPITAL CANTONAL, FRIBOURG, SCHWEIZ (DOZENT DR. E. A. ZIMMER)

SKELETTELEMENTE MEDIAL DES CUNEIFORME I[1]

von

E. A. Zimmer

Am medialen Rand des Cuneiforme I beobachten wir auf dorsoplantaren Aufnahmen gelegentlich kleine überzählige Knochen, deren Anwesenheit wir in letzter Zeit unsere besondere Aufmerksamkeit geschenkt haben, so dass wir nunmehr über eine Beobachtungsreihe von 12 einschlägigen Fällen berichten können. Die Knöchelchen scheinen, soweit man dies aus dem Schrifttum schliessen darf, der Beachtung der Radiologen, Chirurgen und Unfallmediziner weitgehend entgangen zu sein. Sie werden sogar in dem wertvollen Buch von MARTI über akzessorische Knochen nicht angeführt. Wir begrüssen es deshalb, dass DYRE TROLLE 1948 in seiner ausgezeichneten Studie: »Accessory bones of the human foot», die wohl für längere Zeit richtunggebend bleiben dürfte, kurz an diese Skelettelemente erinnert hat. Bei Überprüfung des früheren röntgenologischen Schrifttums konnten wir lediglich drei Autoren finden, die sich — vor mehr als 20 Jahren — mit diesen überzähligen Knochen kurz auseinandersetzten.

Unsere Veröffentlichung über akzessorische Knochen medial vom Cuneiforme I scheint nicht nur aus den eben dargestellten Gründen gerechtfertigt, sondern auch darum, weil dieser kleine Knochen klinisch nicht vollständig belanglos ist, da er röntgenologisch weiterhin falsch gedeutet werden könnte und, nicht zuletzt, weil wir wünschen, dass durch diese röntgenologisch und anatomisch fundierte Mitteilung eine systematische Suche nach Vorkommen und Häufigkeit dieser akzessorischen Knochen angeregt werde.

Die Verwirrung in der Benennung akzessorischer Skelettelemente ist so gross, dass man Mühe hat, für die beiden Knöchelchen überhaupt eine richtige Bezeichnung zu finden. Wir lassen deshalb für den Moment die Frage offen, ob es sich dabei um das Os paracuneiforme, ob es sich um

[1] Bei der Red. am 5. April 1950 eingegangen.

ein Os cuneometatarsale I tibiale handelt oder um einen rudimentären Praehallux. Gerade die letzte Bezeichnung hat zu so verschiedenen Auffassungen geführt, dass wir uns in den Streit der Meinungen über den Praehallux bewusst nicht einmischen.

Bei den überzähligen Skelettelementen, welche in Form kleiner Knochen isoliert und medial von Cuneiforme I nachzuweisen sind, halten wir vorläufig zweckmässig zwei Gruppen auseinander.

Gruppe I: kleine Kalkschatten, gut begrenzt, von verschiedener Form und Grösse, medial vom Zentrum des Cuneiforme I, vollständig isoliert.

Gruppe II: kleine, meist rundliche Knochen, die sich an die Kerbe des Gelenkes zwischen Cuneiforme I und Naviculare I anschmiegen oder in deren Umgebung liegen.

Besprechen wir zuerst unsere *Gruppe I*, also den kleinen Kalkschatten, der medial von der Mitte des Keilbeines I zu liegen pflegt. Bei der Beobachtung unserer Abbildung 1 handelt es sich um doppelseitiges Vorkommen, aber ohne Symmetrie. Man erkennt auf dem Bilde des linken Fusses (Abb. 1 a), dass die mediale Kante von Cuneiforme I im distalen Teil eine eigenartige subkortikale Verdichtungszone zeigt, ähnlich einer arthrotischen Schlifffläche. Im proximalen Teil dieser Kante wölbt sich ein stärkerer Wulst exostosenähnlich vor. In unmittelbarer Nachbarschaft der Kalkanreicherung aber deutlich von ihr getrennt, erkennt man ein 6 mm langes, 3 mm breites ovales Skelettelement, das deutliche Spongiosazeichnung erkennen lässt und in seiner medialen Kante etwas wellig begrenzt erscheint.

Auf der Aufnahme des rechten Fusses (Abb. 1 b) sieht man wiederum eine Verdichtungszone der Medialkante von Cuneiforme I sowie eine exostosenähnliche Vorwölbung, aber in den distalen Abschnitten, während proximal ein kleiner Kalkschatten die Kontur überragt, der, obwohl nicht sicher vom Keilbeinkörper abgrenzbar, doch isoliert zu liegen scheint.

Ein kurzes Wort zu den Formvarianten der Medialkante des Keilbeinkörpers muss hier eingeschaltet werden, da im röntgenologischen Schrifttum auf die eben beschriebenen Veränderungen bis jetzt noch relativ wenig aufmerksam gemacht wurde: Bei der Durchsicht einer grösseren Sammlung anatomischer Cuneiformepräparate konstatiert man immer wieder, dass sich an der medialen Seite Schlifflächen erkennen lassen, die wohl mit einer Sehnenkreuzung in Zusammenhang stehen. Kontrollieren wir unser röntgenologisches Material, so erkennen wir ebenfalls häufig derartige muldenförmige Einbuchtungen, meistens im distalen Abschnitte und darunter markante Kalkanreicherungen der Kortikaliszone (Abb. 2).

Die oben beschriebenen exostosenähnlichen Vorsprünge sitzen manch-

Abb. 1 a. Abb. 1 b.

Abb. 1. Siehe Text.

Abb. 2.

Abb. 3.

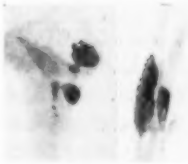

Abb. 4 c. Abb. 4 d.

Abb. 4 a. Röntgenaufnahme des linken Fusses. Der kleine Knochen (↑) ist teils vom Cuneiforme I verdeckt.

Abb. 4 b. Planto-dorsale Röntgenaufnahme des präparierten Fusses. Sehne (↑↑) nach aussen geklappt.

Abb. 4 c + d. Röntgenaufnahmen der Sehnenpartie des M. tibialis ant.

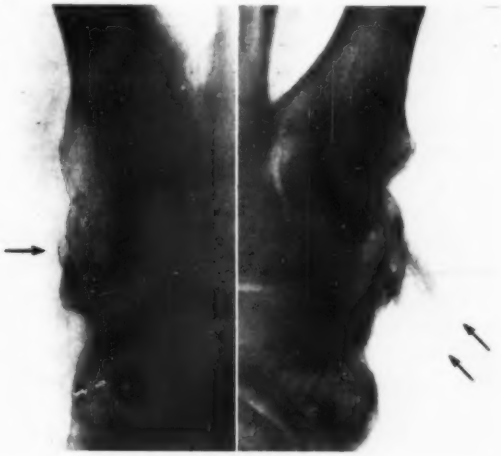

Abb. 4 a. Abb. 4 b.

Abb. 4 e. Photographie des Präparates: der eingelagerte grössere Knochen ist mit einem Pfeil markiert.

Abb. 4 f. Mazerationspräparat.

mal ausserordentlich breitbasig, manchmal jedoch auch zipfelförmig, also typisch exostosenartig, dem Keilbein auf. Man hat bisweilen — z. B. in Fällen, wie unsere Abb. 3 einen zeigt — sogar den Eindruck, als ob eine Sehne distal über diesen Sporn hinwegziehen würde. Die anatomischen Präparate lassen auch deutlich erkennen, dass an der medio-plantaren Fläche des Cuneiforme I zahlreiche solcher Höcker mehr oder wenig scharf begrenzt, breitbasig oder spitz, teils körnig-vielkuppig, vorhanden sind (vgl. Abb. 4 f).

Nach diesen kurzen Bemerkungen über die Formvarianten der inneren Keilbeinfläche kommen wir zurück zur Beschreibung des oder der Knöchelchen, die sich medial dieser Zonen befinden (Gruppe I).

Um unsere Beobachtungen zu erhärten, haben wir mit freundlicher Erlaubnis der Direktoren der Anatomischen Anstalt der Universität Basel, Professor E. LUDWIG, und des Anatomischen Institutes der Universität Fribourg, Professor A. FALLER, das anfallende Sektionsmaterial röntgenologisch daraufhin geprüft. Bei dieser Untersuchung sind wir in Basel auf folgenden Fall gestossen:

Auf einer leider exzentrisch eingestellten dorso-plantaren Aufnahme (mit dorso-anteriorer Schrägprojektion, was wegen der Starre des Präparates nicht anders möglich war) konstatierten wir medial vom Cuneiforme I ausser einer der eben beschriebenen kleinen Exostosen, und zwischen dieser und der Basis von Metatarsale I, einen kleinen Knochen (in Abb. 4 a), welchen wir der weiteren Untersuchung zugänglich machen konnten.

Nach der Amputation des Fusses gelang es uns, Aufnahmen in einer besseren Projektionsrichtung anzufertigen. In Abb. 4 b ist die fragliche Zone nochmals bildlich festgehalten, wobei der Fuss bereits weitgehend anatomisch präpariert war; wie sich am Weichteilschatten ohne weiteres erkennen lässt, ist die Sehne des M. tibialis ant. (↑) nach medial umgeklappt, wodurch sich nahe ihrer Ansatzstelle die (zwei) in Frage kommenden Knochenschatten frei projizieren, so dass sich der Sesambeincharakter sofort offenbart. Durch Einführung eines Zahnfilmes zwischen Sehne und Cuneiforme I ergaben sich die in Abb. 4 c d festgehaltenen Projektionen. In der Sehne befindet sich also nicht nur ein einziges, sondern von den kleinsten Partikeln abgesehen 3 grössere Knochenstückchen eingelagert; das grösste ist 13, das zweitgrosse 6 und das kleine 2 mm lang, und in gleicher Reihenfolge sind sie 4, 3 und 1 mm breit. Innerhalb der Knochen lässt sich deutlich die Bälkchenstruktur der Spongiosa erkennen. Unsere Bilder (Abb. 4 c d) in verschiedenen Strahlengangsrichtungen lassen überdies erkennen, dass die 3 grösseren Skelettelemente vollständig getrennt voneinander liegen, und dass in der Sehne multiple kleine Kalkeinlagerungen enthalten sind, zum Teil ganz winzige Knöchelchen.

Unsere Photographie Abb. 4 e zeigt die hochgeklappte Sehne, die durch präparatorische Längsspaltung in ihren zentralen Partien klafft, so dass aus dieser Lücke der kleine mit Pfeil bezeichnete Knochen hervorschaut. Wir prüften das Präparat, ob sich am Cuneiforme in Höhe der beschriebenen Kalkplatte eine Schlifffläche befinde. Dies war nicht der Fall, wie es übrigens auch die Photographie des mazerierten Präparates (Abb. 4 f) zeigt.

Mit unserer Untersuchung glauben wir den Beweis erbracht zu haben, dass die anscheinend so selten beobachteten kleinen Knochen medial am Cuneiforme tatsächlich vorkommen, auch wenn sie nur stippchenförmig erscheinen, oder wenn sie infolge Superposition nur als kleine Keilbeinexostosen imponieren. Durch die Präparation konnten wir beweisen, dass es sich um Einlagerungen in der Sehne des M. tibialis ant. handelt. Professor E. LUDWIG hatte die Freundlichkeit, das Präparat histologisch zu untersuchen. Sein Bericht lautet: «Das eine Stück besteht aus stark spongiösem Knochen mit weiten, von Fettmark eingenommenen Räumen. An einer Seite setzt eine Sehne an, z. T. an Faserknorpel mit in längeren Reihen eingestellten Zellen. Im zweiten Stück ist der Knochen weniger spongiös als im ersten, ebenfalls fettmarkhaltig. An der Oberfläche liegt hyaliner Knorpel. Ein Sehnenstück strahlt z. T. in den Knochen ein, z. T. in Faserknorpel. Die Bilder entsprechen dem Bau von Sesambeinen. Nekrotische Veränderungen sind nicht nachweisbar.»

Nach diesem Bericht darf man auch eine Myositis ossificans ausschliessen.

Durch unsere Beobachtungen ist sicher festgestellt, dass es sich bei diesem akzessorischen Skelettelement um das bzw. die *Sesambeine des M. tibialis ant.* handelt. Wir wollen deshalb diesen Knochen mit seinen übrigens multiplen Anlagen als *Sesamum tibiale anterius* bezeichnen.

Warum ist dieser überzählige Knochen röntgenologisch so selten beschrieben und anscheinend auch beachtet worden? Die Erklärung ist einfach. Bei einer normalen dorso-plantaren Aufnahme projiziert sich dieses kleine Sesambein, das nahe der Ansatzstelle des M. tibialis ant. an der Plantarseite des Cuneiforme I liegt, in das Keilbein und wird deshalb ganz oder teilweise verdeckt. Bei seitlicher Projektion fällt der Schatten mit jenem des 2. und 3. Keilbeines zusammen. Sucht man diesen Knochen, so ist eine Schrägaufnahme nötig. Man plaziert den Patienten wie bei einer dorso-plantaren Aufnahme und abduziert den Oberschenkel, so dass nur der laterale Rand der Fussohle auf dem Filme liegt. Auf diese Weise gelingt es wohl häufiger, das kleine Sesambein nachzuweisen.

Der zusätzliche Knochen liegt so im Fussgewölbe, dass er mit der Fussunterlage kaum in Berührung kommt, anders liegt aber der Fall bei Individuen, die eine Einlage wegen Plattfüssen tragen. Bei diesen Leuten wird das Fussgewölbe gestützt, fast möchte man sagen untermauert, wo-

Abb. 5 a.

Abb. 5 b.

Abb. 5 c.

Abb. 5 d.

Abb. 5. Kleiner Knochen medial des Gelenkes zwischen Naviculare und Cuneiforme I: Abb. 5 a—c Vergrösserungen. In Abbildung 5 c zeigt sich überdies ein Os intermetatarsale I.

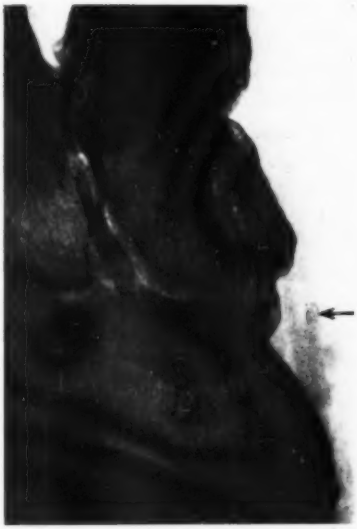

Abb. 6 a.

Abb. 6 b.

Abb. 7 a.

Abb. 7 b.

Bezeichnung: C = Cuneiforme I
N = Naviculare

durch es zu einer Kompression des Knöchelchens zwischen Cuneiforme und Stützeinlage kommen kann. Es ist keineswegs selten, dass solche Patienten im Gebiete des Cuneiforme I über einen unangenehmen Druck ihrer Einlage klagen. Röntgenkontrolle solcher Fälle empfiehlt sich.

Wie haben oben konstatiert, dass das Sesambein unserer Beobachtung manchmal in kleine Kalksplitter aufgeteilt war. Aber auch in der täglichen Praxis beobachten wir nicht selten nur einen stippchenförmigen Kalkschatten medial vom Cuneiforme I, den man nicht ohne weiteres als ein Sesambein diagnostiziert, sondern eher als kleines orthograd getroffenes verkalktes Gefäss, wenn der Patient dafür nicht zu jung wäre.

Die Kalkschatten sind so zart, dass sie sich der Betrachtung vollständig entziehen, sobald die Aufnahmen etwas hart, fast möchte man sagen, sobald diese nicht betont weich exponiert sind.

Als *Gruppe II* bezeichneten wir die kleinen Skelettelemente, die sich der Kerbe zwischen Cuneiforme I und Naviculare anschmiegen, bzw. medial dieser Gelenkfläche liegen. Diese kleinen Knochenschatten sind häufig ebenfalls winzig klein, mitunter ringförmig, manchmal sind sie immerhin zündholzkopfgross und weisen Bälkchenstruktur auf (Abb. 5 a, b, c, d). Doppelseitiges Vorkommen (Abb. 6 a und b) scheint nicht selten zu sein. Aus unserer Bildserie geht eindeutig hervor, dass es sich um echte Skelettelemente handeln muss.

Wir müssen uns nunmehr fragen: Handelt es sich um ein kleines Sesambein, eine isolierte Kapselverkalkung oder um das sog. Os paracuneiforme? Ich neige zur Auffassung, dass es sich um ein Sesambein handelt, vor allem deshalb, weil unsere Bildserie zeigt, dass dieser kleine Knochen relativ weit vom Gelenkverband entfernt ist, während akzessorische Knochen sich normalerweise dem Gelenkverband anschmiegen. Leider hatten wir bis jetzt keine Gelegenheit, dieses Skelettelement anatomisch zu verifizieren. Diese vorliegende Mitteilung soll aber die Aufmerksamkeit auf dessen eventuelles Vorhandensein lenken.

Die Knöchelchen medial der Gelenkfläche zwischen Cuneiforme und Naviculare, bei welchen wir im Moment noch nicht entscheiden können, ob es sich um einen überzähligen Knochen oder um ein Sesambein handelt, können wir vorläufig nur abgrenzen, gegen die selten vorkommenden Ausrisse aus der Basis des Cuneiforme I (Abb. 7 a) oder aus dem Naviculare (Abb. 7 b).

Wenn man sich mit den Skelettelementen medial vom Cuneiforme I befasst, hat man sich mit der bis zum Jahre 1605 zurückreichenden Literatur auseinanderzusetzen, was ausserordentlich mühsam ist, nicht nur wegen der Schwierigkeit der Beschaffung der weitverstreuten und wenig bekannten Zeitschriften, sondern auch wegen der Langatmigkeit der Arbeiten und wegen der seitenlangen Kontroversen. Nachdem wir

uns diesen Studien unterzogen haben, möchten wir hier einen kurzen Überblick geben:

Erstaunlich ist, dass ein berühmter Kenner akzessorischer Skelettelemente, nämlich PFITZNER, sich über akzessorische Knochen medial vom Cuneiforme I vollständig verächtlich aussprach, da er nie einen solchen Knochen entdeckt habe. Er glaubt, nachweisen zu können, dass die Beschreibung dieses überzähligen Knöchelchens auf eine unrichtige Beobachtung, auf einen sich beharrlich fortsetzenden Schreibfehler und auf gedankenlose Nachschrift zurückzuführen sei.

Es entging ihm anscheinend, dass KOHLBRÜGGE, in einer mir im Original leider nicht zugänglichen Zeitschrift, im Jahre 1890 zwischen Cuneiforme I und Metatarsale I einen meist gegen die Plantarseite gelegenen keilförmigen, sich dem Gelenk anschmiegenden Knochen bei Anthropoiden konstatierte, eine Tatsache, die übrigens später HASSELWANDER bei Xylopates-Skeletten bestätigte. Medial vom ersten Keilbein findet man im Tierreich wiederholt akzessorische Knochen, so dass es wohl nicht abwegig ist, auch am Menschenfuss ähnliche Knochen zu vermuten.

Ich vermeide es bewusst, bei diesen Literaturstudien auf den Begriff des Praehallux einzugehen, erinnere aber an die interessanten Arbeiten über den Säugetier-Praehallux von TORNIER 1891 und von NAUCK.

Bei dieser Gelegenheit muss allerdings darauf aufmerksam gemacht werden, dass z. B. das beim Maulwurf vorkommende Sichelbein (Abb. 8) gewisse Ähnlichkeit hat mit einem von BABUCKE beobachteten (Abb. 9) medial vom Cuneiforme I liegenden, gelenkig mit dem Naviculare verbundenen Knochen.

SCHLICHTER hat neuerdings einen ähnlich aussehenden, isolierten Knochen beschrieben (Abb. 10 a), der, im Gegensatz zur Beobachtung von BABUCKE, gelenkig mit dem ersten Keilbein verbunden war. Beim gleichen Patienten fand sich ein kleiner ebenfalls isolierter Knochen in ähnlicher topographischer Lage am anderen Fuss (Abb. 10 b).

Bei flüchtiger Betrachtung haben also die beiden Beobachtungen gewisse Ähnlichkeit dadurch, dass ein längsgestellter Knochenschatten mit einer Gelenkfläche an einem normalen Tarsale artikuliert. Der grundlegende Unterschied besteht aber, wie erwähnt, darin, dass in einem Fall die gelenkige Verbindung mit dem Naviculare, im anderen mit dem (distalen Abschnitt der medialen Kante des) Cuneiforme I besteht.

CALLIER hat 1924 bei einem 19-jährigen jungen Mann einen langsam wachsenden mediolateral verschiebbaren Knochen proximal der Basis vom Metatarsale I exstirpiert. Röntgenologisch zeigte sich dieses Skelettelement an der Innenseite in Keilbeinmitte. Bei der Operation bestand eine gelenkige Verbindung (mit enger Kapsel) dieses Knochens

Abb. 8.
Talpa eur.
(aus NAUCK 1933).

Abb. 9.
Fall von BABUCKE:
N = Naviculare
C = Cuneiforme I
M = Metatarsale I
A = Akzessorische Knochen

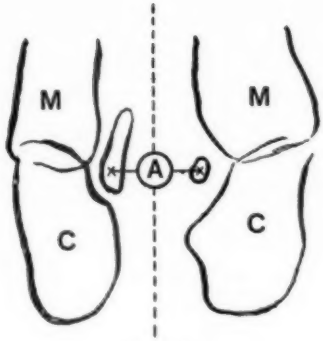

Abb. 10.
Fall von SCHLICHTER:
C = Cuneiforme I
M = Metatarsale I
A = Akzessorische Knochen

mit dem Cuneiforme. Beide Gelenkoberflächen waren mit typischem Gelenkknorpel belegt.

Wie soll man nun diese Knochen einordnen? DYRE TROLLE scheint dabei in gleiche Verlegenheit wie wir geraten zu sein, beschreibt er doch ein Os cuneo-metatarsale I tibiale und setzt dazu (= Praehallux) und ein Os paracuneiforme (= Praehallux, Praecuneiforme). Seine erläuternden Abbildungen zeigen gewisse Ähnlichkeit mit unserem anatomisch untersuchten Fall. Es ist deshalb möglich, dass es sich auch bei seinen Fällen um ein Sesamum tibiale anterius handelt.

Die Studie von DYRE TROLLE, die uns so ausserordentlich wertvoll erscheint, gibt uns aber noch weitere interessante Aufschlüsse. Dieser Autor konstatierte nämlich bei seinen embryologischen Untersuchungen, dass in 13.2 % der untersuchten Fälle medial vom Cuneiforme I eine Knochenanlage erkennbar ist, was er an Hand schöner Schnittbilder belegt. Es sind also in dieser Zone tatsächlich relativ häufig Anlagen zur Knochenbildung vorhanden.

Auf Grund unserer eigenen Untersuchungen und der Literaturstudien ist sicher, dass solche Skelettelemente medial vom Cuneiforme I vorkommen, und zwar häufiger als allgemein angenommen wird. Wegen der Kleinheit, wegen der Schattenarmut und wegen ungünstiger Projektionsverhältnisse sind sie der Beachtung bis jetzt meist entgangen. In ihrer Ätiologie erscheinen diese Knöchelchen verschieden; es gelang uns bei einem solchen Element die Zugehörigkeit festzustellen. Es ist möglich, dass bei Kenntnis dieser Skelettelemente auch unfallmedizinisch

darauf geachtet wird, da deren Anwesenheit klinisch vielleicht doch nicht vollständig bedeutungslos ist.

Wir konnten schliesslich beweisen, dass das als Os cuneometatarsale I tibiale und auch unter anderen Bezeichnungen bekannte Skelettelement tatsächlich einem Sesambein entspricht und deshalb als Sesamum tibiale anterius bezeichnet werden muss, während der proximal davon liegende Knochen nahe dem Cuneiforme-Naviculare-Gelenk gelegentlich auf seine anatomische Zugehörigkeit hin kontrolliert werden sollte, wozu diese Arbeit anregen möchte.

ZUSAMMENFASSUNG

Es wird über Skelettelemente berichtet, die medial vom Cuneiforme I in Form von Akzessorie nachzuweisen sind, wobei ein im distalen Abschnitt gelegenes erstmals anatomisch untersucht werden konnte und sich als Sesamum tibiale anterius entpuppte. An zahlreichen Röntgenbeispielen wird auf diese oft nur andeutungsweise sichtbaren überzähligen Knöchelchen aufmerksam gemacht, die bisher im Schrifttum kaum beachtet waren und vielleicht klinisch eine gewisse Bedeutung erlangen.

SUMMARY

The author describes accessory bones which are localized on the medial side of the 1st cuneiform. For the first time it was possible to examine one of them anatomic; the latter is a sesamum tibiale anterius. Report of several radiological examples of such modifications which were scarcely mentioned at all in the literature and however have a certain clinical importance.

RÉSUMÉ

Description d'os surnuméraires localisés sur le côté tibial du 1er cunéiforme, dont l'un, sis dans la partie distale, est, pour la première fois, examiné anatomiquement. Il s'agit d'un sesamum tibiale anterius. De nombreux exemples radiologiques mettent en évidence ces modifications d'aspect parfois très discret, dont il n'est presque pas fait mention dans les communications anatomiques et radiologiques publiées jusqu'à présent et qui, cependant, revêtent une certaine importance clinique.

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RADIO-IRIDIUM TELETHERAPY[1]

by

H. F. Freundlich, J. L. Haybittle and *R. S. Quick*

Introduction

Soon after the first high power atomic piles began to operate, it was pointed out (1—9) that sufficient quantities of artificial radio-active isotopes would become available to replace radium as a source of γ-radiation for therapeutic purposes. In particular Co^{60} was singled out (1—6) to be a suitable substitute for radium by reason of its long half-life and its convenient mechanical and chemical properties. It could obviously be used either for interstitial treatments, surface application, or as a source for teletherapeutic units. But for the latter application very strong sources are required, and unless a rather large neutron flux is available, it will take a period of a year or more to activate sufficient cobalt for teletherapeutic units, because of the comparatively small neutron capture cross-section of Co^{59} and the long half-life of Co^{60}. It seemed therefore justifiable to investigate the possibilities of other radio-active isotopes which might be equally suitable and yield within a shorter period activities adequate, not only to replace the normal type of teleradium unit, but even to obtain outputs and depth doses comparable with 200—250 KV. roentgen therapy apparatus.

Radio-active isotopes to be used in a teletherapeutic unit, could be specified as follows:

1) The element itself should be cheap and readily available.

2) Its half-life should be long enough to ensure a continuous service without undue complications.

3) The slow neutron capture cross-section should be large enough to produce adequate specific activities in a flux of 5×10^{11} neutrons/cm^2/sec, which is the flux available in the Harwell pile.

[1] Submitted for publication May 1st, 1950.

4) The mean energy of the emitted γ-rays should be above 300 KeV (LEA (10), SPIERS (11)) to obtain the minimum of selective absorption in different types of tissue.

Table 1

Isotopes with Therapeutic possibilities.

Natural Isotope	Natural Abundance	Natural Atom Cross Section (barns)	Type of Radiation of the (A+1) Isotope	Half life of the (A+1) Isotope	Energy of Radiation in Mev of the (A+1) Isotope	
					Particles	γ-rays
$_{21}Sc^{45}$	100%	22	$\beta^-\gamma$	85d	0·36, 1·5	0·9, 1·1
$_{27}Co^{59}$	100%	21·7	$\beta^-\gamma$	5·3yr	0·3	1·1, 1·3
$_{55}Cs^{133}$	100%	25·6	$\beta^-\gamma$	1·7yr	0·65	0·58, 0·78 1·35.
$_{63}Eu^{153}$	52·23%	390	$\beta^-\gamma$	5–8yr	0·34, 0·84	1·4 et. al
$_{69}Tm^{169}$	100%	106	$\beta^-\gamma$	105d	0·98	0·83
$_{73}Ta^{181}$	100%	20·6	$\beta^-\gamma, e^-$	117d	0·51	1·13, 1·22
$_{77}Ir^{191}$	38·5%	388	$\beta^-\gamma, e^-$	70d	0·59	0·47, et. al.

Table 1 shows a number of isotopes which deserve closer consideration.

Before assessing the different merits of the isotopes shown in this table, a brief explanation should be given of how the activity of an isotope produced in an atomic pile can be calculated.

When saturation is reached the number of atoms/gram disintegrating per sec. must be equal to the number of neutrons captured per sec. In other words the specific activity, *i. e.* activity per gm will then be:

$$S_0 = \Phi \times n \times \sigma \text{ (disint./sec/gm)}$$

$$S_0 = \frac{\Phi \times N \times \sigma}{A}$$

$$S_0 = \frac{\Phi \times N \times \sigma}{A \times 3.7 \times 10^{10}} \text{ curie/gm}$$

Φ = neutron flux/cm²/sec.

n = number of atoms per gm

σ = neutron capture cross-section (cm²)

N = Avogadro's Number 6.02×10^{23} (atoms/gm/atom)

A = atomic weight.

As in the case of natural radio-activity, this activity is built up in time according to an exponential law. So the activity at any time after insertion into the pile is:

$$S = S_0\left(1 - \exp. -\frac{0.693\ t}{T}\right) \text{ curie/gm.} \qquad T = \text{half-life.}$$

$$S = \frac{\Phi \times N \times \sigma}{A \times 3.7 \times 10^{10}}\left(1 - \exp. -\frac{0.693\ t}{T}\right) \text{ curie/gm.}$$

Going back to Table 1, the two rare earth elements Eu and Tm can be dropped immediately on account of their scarcity. On the other hand, Ir^{191} stands out by its very large neutron capture cross-section and deserves therefore closer investigation.

Going through the four specifications laid down above, iridium certainly fulfils condition No. 1.

With regard to condition No. 2, it is quite feasible to achieve a continuous service with two identical sources per unit, one in use, the second being reactivated in the pile at the same time. After a month both sources are exchanged. Source No. 2 is used in the therapeutic unit, Source No. 1 is reactivated in the pile. During the month in use an Ir^{192} source decays by about 25 %. But this fact can be easily taken into account when calculating the appropriate treatment time.

With regard to condition 3 the larger cross-section of iridium is the main advantage of using iridium in preference to cobalt. Table 2 shows the specific activities which can be obtained with a neutron flux of 5×10^{11} neutrons/cm²/sec. This table also shows the comparative figures for tantalum, which would be preferable to cobalt if only activation times under one year are considered.

Table 2

Specific Activities (curie/gm) obtained after different times of irradiation.

	30 days	90 days	180 days	1 year	5 years	S_0
Co^{60}	0.023	0.092	0.161	0.276	1.11	2.3
Ta^{182}	0.150	0.380	0.604	0.815	0.92	0.92
Ir^{192}	4.23	9.6	13.5	15.8	16.3	16.3

Condition No. 4 is certainly fulfilled, as the mean energy of the emitted γ-rays is about 0.4 MeV (see part III). From Fig. 1 it will be seen that at energies greater than 0.3 MeV the relative energy absorptions for bone, muscle, fat are constant so that it would be expected that radiations within this region would behave similarly, in particular, the γ-rays from Ir^{192} and Ra (B + C) should be comparable. However, the lower energy of the γ-rays of Ir^{192}, compared with those of Ra (B + C),

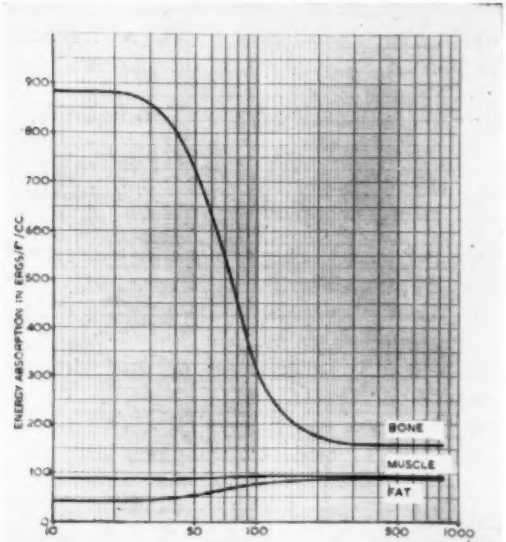


Fig. 1. Relative energy absorption in tissues: adapted from Spiers (ii).

simplifies the problem of protection considerably. As can be seen from the table of absorption coefficients published by GENTNER (17), the total absorption coefficient in lead for 0.4 MeV is about 2.5 times larger than the absorption coefficient for 0.8 MeV. This is mainly due to the rapid increase of the photoelectric absorption coefficient just in this energy region.

Taking all these facts together, the authors thought it worth while proceeding with the actual construction of a teletherapeutic unit, using Ir^{192} as the source of γ-radiation. Details of this construction are described in the next and the physical measurements in the last part.

Before concluding this introductory chapter, a few words should be said about the activity required for a practical unit, and how this activity is obtained under practical conditions.

When planning this unit it was decided to aim at an intensity of 10 r/min at an F.S.D. of 8 cm which is of the order of that of a 5 gm/radium unit. As Ir^{192} emits only one γ-photon per disintegration (14), whereas radium and its disintegration products emit two photons (EVANS (15)) it seemed reasonable to aim at about a 10 curie iridium source.

Unfortunately, in practice, there are various factors which considerably upset the calculations of activity according to the above formula.

Firstly, the pile is not necessarily operating at constant power, which means that the pile flux of 5×10^{11} neutrons/cm²/sec is not maintained during the whole period while the iridium is irradiated.

Secondly, the actual shape of the source has a great effect on the final activity:

a) Owing to the very large cross-section of iridium, the neutron flux itself is reduced at the point where the iridium is exposed. The figure given for the neutron flux is partly due to neutrons crossing this area more than once. But if a material with a large cross-section is deposited at this particular point, the neutrons have a large probability of being captured at the first crossing and they will therefore not be able to cross this area for a second time.

b) Again because of the large cross-section, neutrons will not be able to penetrate into any depth of a thick sample, which means that only the outer layers of a disc would be activated, and only a fraction of the exposed material would become radioactive.

In order to overcome all these difficulties a larger amount of iridium was actually irradiated than seemed necessary according to the calculations. Furthermore, the iridium source itself consisted of four concentric rings, 0.1 mm thick, which were irradiated at separated places in the pile in order to keep the reduction of the neutron flux at a minimum. With these precautions an intensity of 13 r/min at 8 cm F. S. D. was obtained after an irradiation of 11 weeks. This irradiation was interrupted half way through for three weeks in order to carry out some measurements. The total weight of the iridium rings was 4.4 gm.

Finally, a few words have to be said about Ir^{194}. Each natural sample of iridium consists of Ir^{191} with an abundance of 38.5 % and Ir^{193} with an abundance of 61.5 % (13). Ir^{193} has also a large neutron capture cross-section and it becomes Ir^{194}, which has a half-life of 20 hrs. Initially there are two strong activities, that of Ir^{192} and that of Ir^{194}. It is therefore essential to wait about 4—5 days to give Ir^{194} a chance to decay before loading the iridium rings into the teletherapeutic unit.

Design and Construction

Probably one of the major problems in the design of large teleradium units is the provision of adequate protection for staff, especially during the period while patients are being set-up for treatment. It has now become almost standard practice to store the radium in a properly protected safe from which it is mechanically (usually pneumatically) transferred to the »head» for the time of treatment only, and after the staff have left the treatment-room; this enables the weight and size of

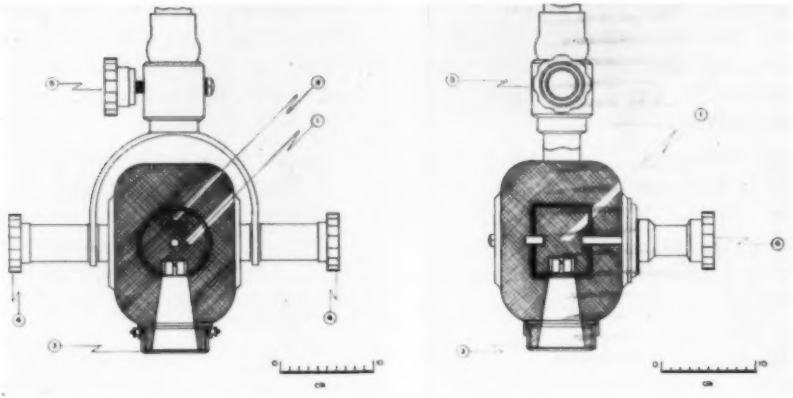


Fig. 2. Sectional views of unit.

the head itself to be considerably reduced, so facilitating accurate adjustment to the patient.

The preceding discussion has shown that, using iridium as the source of radiation, adequate protection of a teletherapy unit giving an output comparable with that of a normal teleradium unit should be possible without removal of the source from the head between treatments, and with the consequent simplification due to the absence of the complicated mechanism required for this purpose. The principal conditions to be fulfilled by the design are as follows:

(1) the radiation output and dose distribution to be similar to those from a 5 gm radium unit; in particular, a dose-rate at the surface of the applicator of about 10 r per minute.

(2) the head should be suitable for mounting on a normal type of roentgen tube stand.

As the unit was to be used in a typical roentgen treatment room lined with 6 mm of lead and only approached closely during the actual setting-up of patients a dose-rate in excess of tolerance could be permitted on the surface of the head with the beam cut-off.

In order to obtain the necessary information about radiation quality, intensity and especially lead absorption data for the final design, preliminary investigations were made with a simple unit of small activity. The source in this case was an iridium disc, of diameter 2 cm, thickness 0.5 mm backed by a 1.5 mm thick copper disc mounted in a large lead block with a tapering aperture giving a field diameter of 5 cm at a distance from the source of 8 cm. When not in use, the aperture was closed

by a 5 cm thick lead block. The arrangement used is shown diagrammatically in Fig. 5, and the results obtained are discussed on p. 10.

A minimum output of 10 r per minute at the F. S. D. of 8 cm was chosen as a suitable value for clinical purposes to avoid excessive treatment times, and on this basis and using the lead absorption curves obtained (Fig. 7) the transmitted intensities and distances for various tolerance levels are as follows:

Table 3

Lead Thickness (cm)	Transmission		Distance (cm) from source for	
	(%)	r/hr at 10 cm	Tolerance	Daily Tolerance in 1 hr.
0	100	384	—	—
2.0	1.75	6.72	—	—
2.5	0.90	3.45	—	—
3.0	0.45	1.73	112	42
3.5	0.25	0.96	83	31
4.0	0.15	0.575	64	24
4.5	0.10	0.384	52.5	20
5.0	0.05	0.192	37	14
8.0	0.0036	0.014	10	—

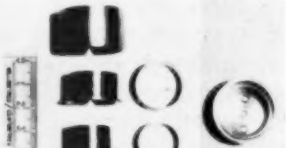
The »Tolerance Dose» is taken as 0.5 r per week of 35 working hours.

As a suitable compromise a minimum lead protection of 5 cm was chosen, the general design of the head being shown on Fig. 2. Any form of movable lead shutter was rejected as likely to make the unit excessively large and complicated and instead the source 2 is mounted on the outside of a lead cylinder 7.5 cm diameter 1 which rotates inside a larger lead block of cylindrical section 12.5 cm diameter and 17 cm long, with hemispherical ends. In the OFF position (as shown dotted) the aperture is shielded by the thickness of the smaller cylinder, which for use is turned by handle 6 so that the source is in line with the port, and spring loaded plungers ensure the exact location of the source in both positions.[1] The unit is carried by a stirrup, rotation of which is locked by knob 5 and movement in the plane of the axis of the beam is controlled by knobs 4; for increased safety knobs 4 and 6 are fitted to extension handles at a distance of 10 cm from the outside of the lead block.

The maximum size of field with this unit is a circle 5 cms in diameter, and detachable lead applicators 3 are provided for different field dimensions. The outer end of each applicator is closed by a disc of 0.25 mm copper and a perspex disc to remove soft radiation scattered from the lead aperture.

[1] While this paper was in preparation a proposed design of a similar type for use with a radiocobalt source was published by Coliez (6).

Fig. 3. General view of unit.



(a) (b)

Fig. 4. Source showing:
a) Method of mounting rings.
b) Rings assembled.

The design of the source itself must provide for the maximum mass of iridium, so as to give the required activity, within small dimensions and at the same time ensure the minimum self-shielding during irradiation (see page 5); also handling of the active source during loading must be reduced to a minimum. For these reasons the construction shown in Fig. 4 was adopted. The complete source is made up of four rings of 0.1 mm thick iridium mounted for mechanical strength on aluminium bases, the diameters of the rings being 1.1, 1.4, 1.7, 2.0 cm respectively. The rings are enclosed and accurately located in an aluminium cylinder, the whole assembly being retained by a single screw; the front face of the cylinder is 1 mm thick.

Apart from its advantages for activation and assembly this construction permits simple modification of the resulting isodose distribution by appropriate adjustment either of the height and hence the irradiated mass of the iridium rings, or by unequal irradiation of individual rings. In the present case all rings were activated equally and it was later found (see p. 15) that the isodose curves descend to a greater depth near the geometrical edge of the beam. This was easily corrected by an additional annular filter but it would obviously be a simple matter to provide such adjustments by the rings themselves.

Measurements of depth doses at increasing focal-skin distances (Fig. 13) show that with a source-skin distance of 25 cm it would be possible to obtain depth doses comparable with those obtained from 220 KV roentgen therapy apparatus and 50 cm F.S.D. The radiation output is then 1/10 of that at 8 cm, in very close agreement with the inverse square law, so that to maintain the output at the present level a source of 10 times

the original strength, *i. e.* approximately 100 curies, will be necessary, and correspondingly increased protection would have to be provided.

Recently SPIERS & WILSON (16) have reported the use of uranium metal as screening material for large teleradium sources and it seemed worth while to consider the possibilities of uranium in this case. In the absence of any measured absorption data for iridium gamma rays in uranium a tentative theoretical estimate has been made of the probable absorption curve to be expected; no great accuracy is claimed for this but it is unlikely to be so far out as to invalidate these general predictions.

The linear absorption coefficient may be written

$$\mu \ (\text{cm}^{-1}) = \frac{\varrho Z N}{A} \left[{}_{\text{a}}\sigma + {}_{\text{e}}\tau \right]$$

where ϱ = density of material (gm/cc)
Z = atomic number
A = » weight
N = Avogadro's number (6.02×10^{23} atoms per gm atom)
${}_{\text{e}}\sigma$ = Compton absorption coefficient per electron
${}_{\text{e}}\tau$ = Photoelectric absorption coefficient per electron.

Values of ${}_{\text{a}}\sigma$ are taken from GENTNER's table (17) and ${}_{\text{e}}\tau$ is estimated from the corresponding figures for lead assuming a third power law of variation with Z; this again is probably not strictly accurate but is unlikely to alter the order of the results (see, for example, MAYNEORD & CIPRIANI (4)). A transmission curve is then calculated

(a) by modification from the lead absorption curve

(b) from the spectral distribution found to fit the lead curve very closely (see p. 13).

It will be seen from Fig. 7 that there is quite close agreement between the curves calculated in both ways, the same divergence at greater thickness being shown as in the case of the lead curve[1].

With the design of head as used in the present unit the weight is given fairly accurately by

$$W \ (16) = 0.01615 \ [(t + 1.35)^2 \ (t + 1.5)] \varrho$$

where t = thickness of protection material (cm)
ϱ = density » » » (gm per cc)

and the weights of head for the present and large units in both lead and uranium are:

[1] Subsequent experimental values are in close agreement with the calculated transmission curve.

Table 4

Nominal strength (curies)	Lead		Uranium	
	Thickness	Weight	Thickness	Weight
	cm	lbs	cm	lbs
10	5.0	48	2.6	20
100	7.3	120	3.8	43

The use of uranium would thus appear to effect quite a considerable saving in weight and would enable even the large unit to be mounted on a small roentgen tube stand. Alternatively a small unit could be made completely protected (that is, the dose at the surface of the head not exceeding tolerance) and still have a weight of the order of 50 lbs. only. A further possibility which is being considered is the use of a hollow construction giving a greatly improved volume/weight ratio.

Physical Measurements

All ionisation measurements, except where otherwise stated, were made with a standard 25 r Victoreen chamber calibrated at the National Physical Laboratory for radium γ-rays and for roentgen rays of half-value layer 2 mm of copper. The walls of the chamber were 0.75 mm thick and the γ-ray calibration was made with the chamber surrounded by a 2 mm air wall sheath. A preliminary experiment using a perspex chamber of variable wall thickness on a Victoreen stem, showed that for the γ-rays from iridium a wall thickness of 0.75 mm was sufficient. As the Victoreen calibration only altered by 4 % between the roentgen and γ-ray regions, no appreciable error was involved in using the chamber as calibrated for a quality of 2 mm Cu. H. V. L.

Quality

The absorption curves in copper and lead (Fig. 6) were measured using an activated iridium disc 2 cm in diameter as source. The disc

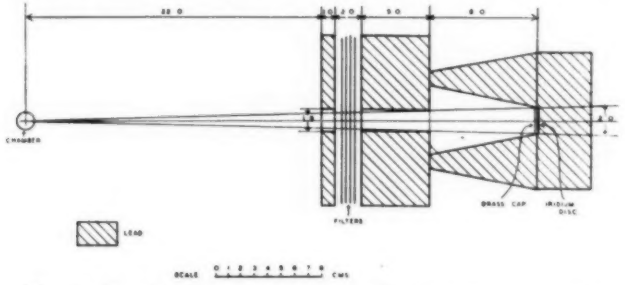


Fig. 5. Experimental set-up for absorption measurements.

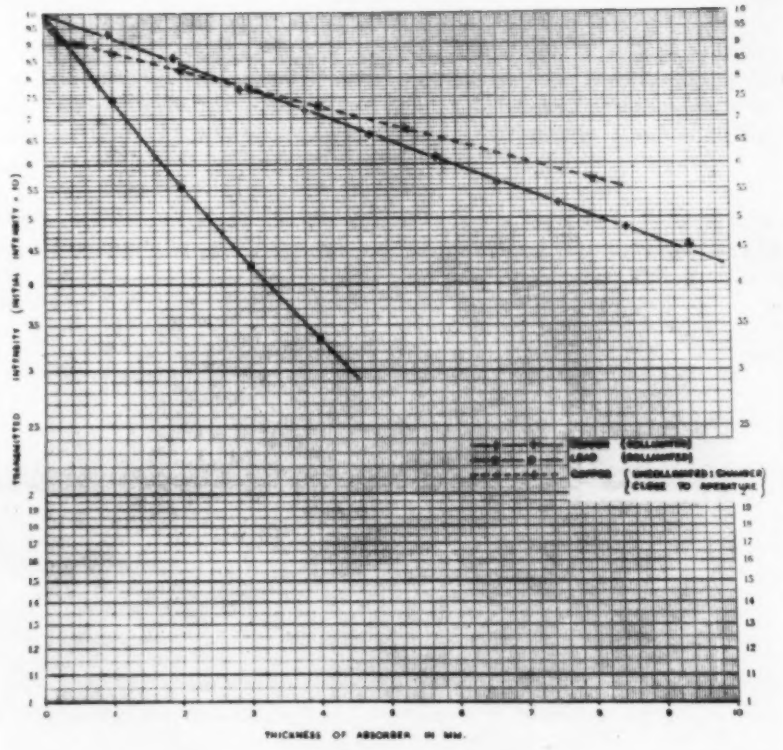


Fig. 6. Absorption in thin filters.

was covered by a brass cap of sufficient thickness to absorb the β emission, and the experimental arrangement to produce a collimated beam is shown in Fig. 5. The half-value layer of the γ-radiation in copper was

Table 5

Half-value layer	Source of absorption data	Mean energy KeV
2.4 mm lead	Gentner (experimental) (17)	400
	Gentner (theoretical) (17)	375
	Robley D. Evans (18)	370
8.1 mm copper	Mayneord & Lamerton (19)	380
	Greening (20)	400

found to be 8.1 mm and in lead 2.4 mm. To derive the mean energy from these figures, various absorption data may be used, and the results using different sets of data are shown in Table 5.

It will be seen that the mean energy is in the region of 400 KeV, a value considerably lower than the previously published figure of 0.52 Me (21). It is difficult to find any explanation for this discrepancy, except the possibility that the previous workers used a poorly collimated beam. We have found that with poor collimation higher half-value layers can be obtained, and consequently higher values for the energy. An example of this is shown by the dotted curve in Fig. 6, which was obtained

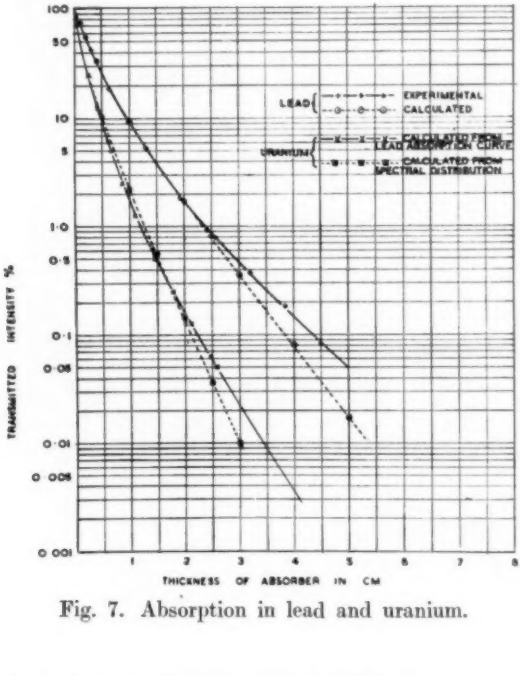


Fig. 7. Absorption in lead and uranium.

with the chamber close to the aperture of the unit and no collimation. After the soft component scattered from the lead walls has been removed by 0.25 mm copper, the curve straightens out to give an apparent half-value layer of 11.3 mm Cu. In the actual unit the soft radiation from the walls was eliminated by fitting across the ends of the applicators permanent filters of 0.25 mm Cu.

The absorption in thick lead, already mentioned (Fig. 7) was investigated with the disc source referred to above, using as detector a large

monitor chamber designed for protection measurements, capable of reading down to one milliroentgen/hour.

Various gamma ray spectra of Ir^{192} have been published (22—25), and an attempt has been made to fit several of these to the experimental curve. The best agreement was obtained with energies of 307, 467 and 605 KeV (MANDEVILLE & FULBRIGHT (22)) present in the proportion of 55, 22 and 23 % of the total respectively. The curve in Fig. 7 calculated from this distribution is in good agreement with the measured curve down to a thickness of 2 cm. The discrepancy at greater thicknesses may be caused by the experimental errors due to scattered radiation making up a larger proportion of the low dose-rates being measured. Work is in hand to investigate this region more accurately.

Table 6

Radiations	Filter	Half-value layer
Roentgen rays		
220 KV peak	1 mm Cu + 1 mm Al	1.5 mm Cu
400 KV peak (18) ...	4 mm Cu	4.5 mm Cu
1,000 KV peak (26) ...	2 mm Pb + 2 mm Al	9.3 mm Cu
γ-rays		
Radium (27)	—	7.5 mm Pb
Iridium	—	2.4 mm Pb 8.1 mm Cu

The half-value layers in Table 6 show that the output of the iridium unit is similar in quality to that of a 1 MeV roentgen machine.

Half-life

The decay of an activated iridium disc was measured over a period of a month, and was found to correspond to a half-life of 70 ± 3 days (13). No evidence of the short-lived Ir^{194} could be detected four days after removal from the pile.

Protection

The monitor chamber referred to above, was also used to measure the distribution of radiation around the unit (Fig. 8). It will be seen that in the OFF position, the tolerance level is reached 38 cm from the lead *i. e.*, 43 cm from the iridium, and the dose 10 cm from the lead is 7 times tolerance, in reasonable agreement with the values predicted from the absorption curve. In the ON position, the operator is below tolerance level as long as he is farther than 210 cm away at the side of the unit, or farther than 70 cm away directly behind it.

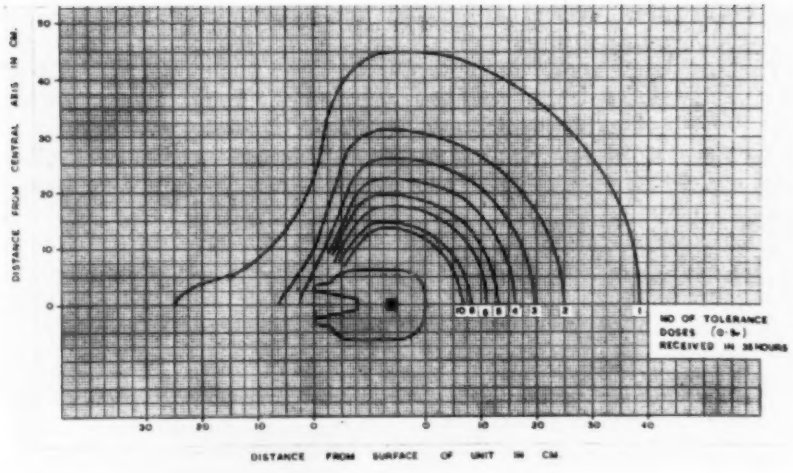


Fig. 8 a.

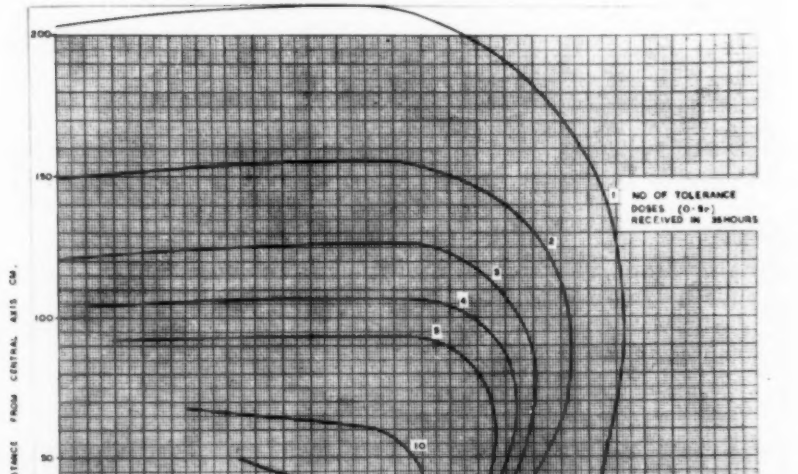


Fig. 8 b.

Fig. 8. Distribution of radiation around unit in a) OFF, b) ON position:

Dosimetry

Depth dose measurements were made in a perspex sided water phantom, $20 \times 20 \times 30$ cm. (Preliminary investigations showed that this was large enough for the field sizes used.) The chamber was surrounded by a closely fitting perspex sheath when in the water, while for surface readings it was half sunk in a hollow in the front wall of the phantom, the readings being corrected for the gap between applicator and phantom by means of the measured variation of the dose in air on the central

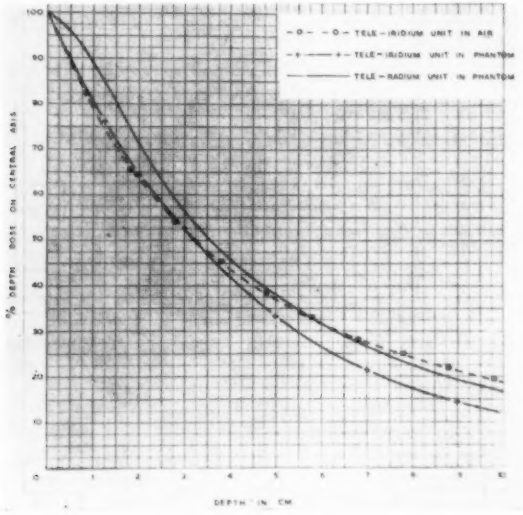


Fig. 9. Depth dose curves on central axis. F. S. D. 8 cm. Field diameter 5 cm.

axis (Fig. 9). On this same graph are shown the central axis depth dose in the phantom for a 5 cm diameter field, and a depth dose curve for a 5 gm teleradium unit working under similar conditions (28). These two curves compare favourably, the doses from the iridium unit being only from 4 to 7 % lower than those from the radium unit.

The isodose curves for a 5 cm diameter and a 3 cm diameter field are shown in Figs. 10 and 11. It should be noted that near the edges of the field these can only be approximate owing to the size of the chamber. The concentric ring form of the source used in the unit resulted in a kink in the curves for the larger diameter field as shown by the dotted 10 % isodose curve in Fig. 10. This was eliminated, and the final shape obtained, by fitting across the aperture an extra annular filter of copper 1 mm thick and of internal diameter 3 cm.

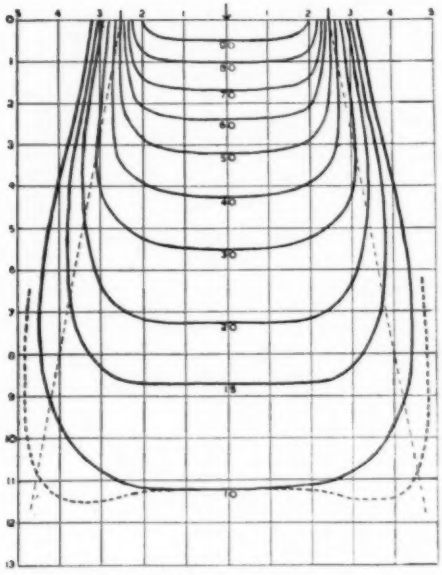


Fig. 10. Isodose distribution: F. S. D. 8 cm. Field diameter 5 cm.

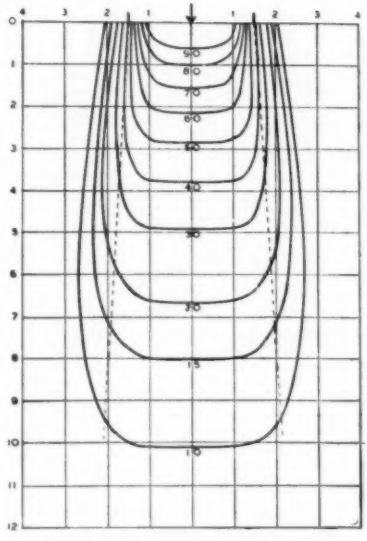


Fig. 11. Isodose distribution: F. S. D. 8 cm. Field diameter 3 cm.

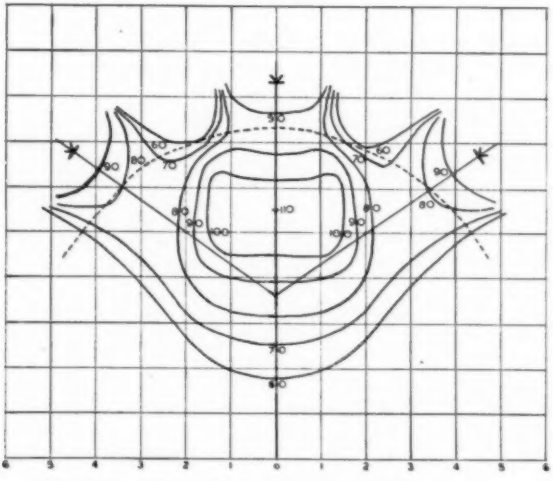


Fig. 12. Three-field treatment of ca. larynx. All fields 3 cm. in diameter.

Fig. 12 shows a specimen dose distribution obtained in a possible three field technique for treatment of the larynx. The dimensions are similar to those published by Wilson (29) for a teleradium technique used at the Westminster Hospital, and comparison shows that the ratio of skin to tumour dose is almost the same in both cases, being 0.88 for the iridium, and 0.91 for the radium unit. If a tumour dose of 6,000 r was required at the 100 % contour in an overall time of 6 weeks, then the decay of the source could be allowed for in any of the following three ways:

a) The time could be adjusted each day to give a constant daily dose of 200 r.

b) A fixed time could be used for each of the five treatments in any one week, so as to give a constant weekly dose of 1,000 r.

c) The daily time could be kept constant throughout.

In Table 7, the details for one field using each of these three methods are shown, assuming a dose rate on the first day of treatment of 13 r/min.

Table 7

Week No.	(a)		(b)	(c)
	r/min. on first day of week	Time (mins.) on first day of week	Daily time to give 1,000 r each week	Weekly dose giving 18.6 mins. each day throughout
1	13.0	15.4	15.7	1,183
2	12.1	16.5	16.9	1,101
3	11.3	17.7	18.0	1,030
4	10.5	19.0	19.4	955
5	9.85	20.3	20.7	897
6	9.15	21.8	22.3	834

As it is proposed to reactivate the source each month, the times for the 5th and 6th weeks would in practice have to be recalculated for the new source.

To obtain information for the design of a possibly larger unit (see p. 122) the percentage depth doses at 5 cm and 10 cm depth below the surface were measured for different focal-skin-distances (Fig. 13). The field size was kept constant (5 cm diameter) by means of a lead aperture 3 cm thick placed on the surface of the phantom, while the iridium unit was stood off the appropriate distance to give the required F. S. D.

Finally, it is interesting to consider the effect of the absorption of the iridium γ-rays in a heterogeneous medium as occurs in practice. SPIERS [(11) Fig. 10] has given an illustration of a beam passing through the lower jaw, and as this unit is likely to be used mainly for treatments

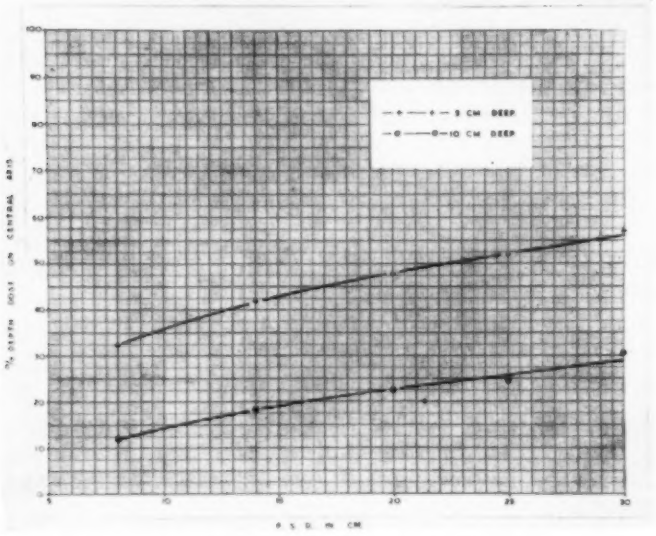


Fig. 13. Variation of depth dose with F. S. D. Field diameter 5 cm.

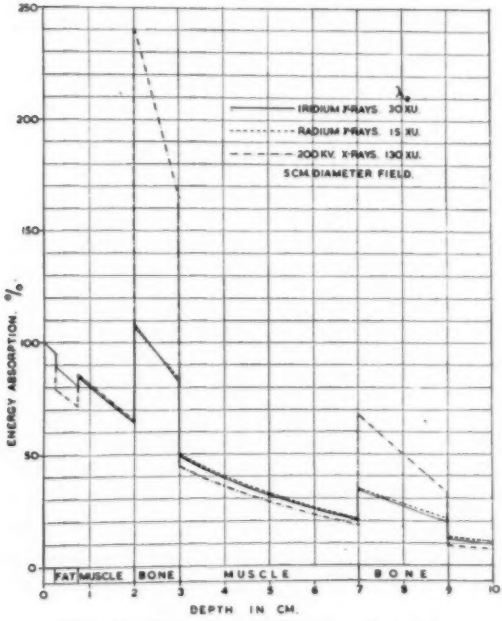


Fig. 14. Comparative energy absorption.

around the head and neck, this example is particularly applicable. Following his, admittedly approximate, but very instructive analysis, similar calculations have been made for gamma rays of mean energy 400 KeV and the relative energy absorption compared with that for radium γ-rays and 200 KV roentgen rays. The depth dose curve for a 5.0 cm diameter field with the iridium unit is used as the basis for these calculations. The curve quoted by SPIERS for the Leeds Radium Beam unit agrees very closely with this after a depth of 3 cm and in 200 KV medium-distance techniques very similar values are obtained (30). It will be seen (Fig. 14) that the divergence between radium and iridium γ-rays is very small, in striking contrast with the behaviour of 200 KV roentgen rays.

Acknowledgements

The authors are indebted to members of the Isotope Division of the A. E. R. E., Harwell, in particular to Mr. W. S. Eastwood, for much helpful advice and co-operation, to Mr. V. D. Martin for building the unit, and finally to Professor J. S. Mitchell for his continued interest in the work.

SUMMARY

The possibilities of Ir^{192} as a source of γ-rays for teletherapeutic units have been investigated, and the design of a complete unit is described. An output of about 11 r/min. at 8 cm f. s. d. is obtained from a unit weighing approximately 50 lbs., which nevertheless has sufficient lead protection to make pneumatic control unnecessary. Measurements of protection, absorption, and dose distribution have been made. Future developments leading to improved design and increased output are discussed.

ZUSAMMENFASSUNG

Die Möglichkeiten des Ir^{192} als Quelle für Gammastrahlen in teletherapeutischen Apparaten wurden untersucht, und es wird ein Plan für ein vollständiger Apparat beschrieben. Eine Ausbeute von etwa 11 r/Min. auf 8 cm Fokus-Haut-Abstand wird mit einem Apparat erhalten, der etwa 22—23 Kg wiegt und trotzdem so gut bleigeschützt ist, dass sich eine Luftdruckkontrolle erübrigt. Messungen des Schutzes, der Absorption und der Dosisverteilung sind gemacht worden. Zukünftige Entwicklungsmöglichkeiten, die zu besserer Konstruktion und grösserer Ausbeute führen, werden besprochen.

RÉSUMÉ

Les auteurs ont étudié les possibilités qu'offre l'Ir^{192} en tant que source de Rayons gamma pour des appareils de télécuriethérapie, et décrivent le modèle d'un appareil complet de ce genre. On obtient un rendement d'environ 11 r. min. à une distance de la source à la peau de 8 cm avec un appareil pesant approximativement 22—23 kg, qui cependant est suffisamment protégé par du plomb pour rendre superflu un contrôle pneumatique. Des mesures de la protection, de l'absorption, et aussi de la distribution des doses ont été faites. Les auteurs discutent des développements ultérieurs pouvant améliorer le modèle et accroître le rendement.

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FURTHER EXPERIMENTAL INVESTIGATIONS OF INJURIES FROM CONTRAST MEDIA IN CEREBRAL ANGIOGRAPHY[1]

Summation of Various Injurious Factors

by

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In earlier experimental studies (BROMAN and OLLE OLSSON, 1948, 1949) it was shown that various contrast media of the diodrast group and intended for use in cerebral angiography are capable of injuring the cerebral vessels of laboratory animals. The injuries were manifest in the form of a disorder in the permeability of the cerebral vessels, edema, stasis, and punctate hemorrhages. An impairment of the permeability only is the mildest form of such injuries. It was observed that the incidence and the degree of severity of the vascular lesions varied according to the concentration of the medium used and to the application time, *i. e.* the time the medium was allowed to act upon the cerebral vessels.

In clinical cerebral angiography the contrast medium often comes into contact with blood vessels in areas with pathologically altered brain tissue. We therefore thought it of interest to try to find out whether other factors might play a contributory part in the causation of disorders or lesions to the cerebral vessels incidental to cerebral angiography. It was thought that under certain pathological conditions through a summation effect otherwise non-injurious concentrations and application times of the contrast agents would be capable of damaging the cerebral vessels. The present study is based on this hypothesis.

In the present investigation contrast media used for cerebral angiography were injected into laboratory animals via the carotid artery.

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Contrast media of a rather low toxicity were selected (umbradil, umbradil forte). In order to study a possible summation effect of injurious agents the following tests were made.

1. Repeated injections of one and the same contrast medium administered at certain intervals, whereby each injection was given for an otherwise non-injurious application time.
2. Temporary blockade of the arterial circulation in the brain.
3. Simultaneous effect of another chemo-toxic factor of a concentration below that at which it is otherwise liable to cause manifest damage.

Technique

The injection technique and the manner adopted for the recording of disorders in the permeability of the cerebral vessels is described in our above-mentioned earlier papers. In the first experimental series of the present investigation the injection was made into the carotid artery, the solution being supplied by means of a rubber tube and a cannula from a reservoir, which could be elevated. In this manner the application pressure was varied according to the prevalent blood pressure.

Results

1. *Repeated injections of one and the same contrast medium via the carotid artery.*

The purpose of this series was to find out whether a sequence of several injections of contrast medium of non-injurious concentration applied for a non-injurious period was capable of damaging the cerebral vessels. As contrast medium we chose umbradil (Astra) which had been found in earlier studies to be non-injurious even in association with prolonged application (40 secs.).

The medium was applied in the manner described above via the carotid artery, whereby the application time of every individual injection never exceeded 30 secs. The experiments were carried out on cats and rabbits narcotized with dial and ethyl urethane respectively. The animals were given repeated injections of one and the same contrast medium at intervals varying from one experiment to the other. The results are shown in table I.

The table shows that when the injections were given in sufficiently rapid succession (at intervals of a few minutes) a summation effect was produced in the form of a typical disturbance of the permeability of the cerebral vessels on the injected side. In the positive tests the damage consisted solely of a disorder in the permeability of the vessels (cf.

Table I

Nr.	Animal	Nr. of injections	Interval between injections	Symptoms	Impaired permeability
1	Cat	3 inj.	30 min.	Shock 15—20 min. after first inj.	—
2	»	4 »	15 »	Shock 15—20 min. after first inj.	—
3	Rabbit	3 »	15 »	Shock 15—20 min. after first inj.	—
4	Cat	4 »	1—2 »	Clon. contralat. conv. after second inj.	+
5	Rabbit	4 »	1—3 »	—	+

results of the injection of umbradil forte — BROMAN and OLLE OLSSON, 1948—49).

It should be added that hitherto we had conceived the occurrence of unilateral clonic convulsions as a sign of a cerebral injury following damage to the vessels. The correctness of our assumption was supported by the fact that in the present series such cramps were seen in one of the two positive cases. On the other hand, it should be mentioned that in one exceptional case (not included in the table) such cramps occurred already after the first injection of 35 per cent umbradil applied for 30 seconds. As we regarded this so remarkable, we decided to control whether a disturbance of the vascular permeability really had occurred and therefore terminated the experiment with the dye test without giving the animal any more injections. The result was, however, negative, which thus shows that the convulsive effect of the contrast medium need not necessarily comprise vascular injury with demonstrable disturbance of the permeability.

2. *Transient arterial blockade of the cerebral circulation with a simultaneous injection of contrast medium into the carotid artery.*

The purpose of the present experimental series was to control whether retardation of the cerebral circulation can favour the arisal of a vascular injury incidental to the injection of a contrast medium. That this should be the case was to be expected, because such a blockage would naturally prolong the application time. The ischemia and anoxia following the blockade of the circulation might, of course, also be expected to contribute towards the possible arisal of a vascular injury, but earlier studies (BROMAN, 1949) showed that this possibility need not be taken into account, because the cerebral blood vessels are very resistant to anoxia.

The cerebral circulation was retarded or shut off by clamping the cerebral arteries in experiments on cats narcotized with dial (cf. POLLOCK and DAVIS, 1923): a silver clip was fastened to the basilar artery after trephination of the base of the skull, ligation of the carotid artery of the injected side and temporary compression of the carotid artery of the other side. As the soft parts of the neck, except the jugular veins and the trachea and the two carotid arteries, were strangled, temporary compression of the non-ligated carotid retarded the cerebral circulation

considerably. By giving a trial injection of physiologic saline into the carotid artery we could see through the trephination over the hemisphere of the injected side that the blood did not return into the pial vessels until 15 to 30 seconds after termination of the injection. Hence, even with a very brief injection time the solution presumably remained in the cerebral vessels 15 to 30 seconds. The application time thus prolonged might be expected to produce a damage in association with the use of contrast media whose injurious application time is about 10 to 15 seconds (*e. g.* umbradil forte, 50 p. c.), whilst no damage could be expected from the use of such slightly toxic contrast media as 35 per cent umbradil, which in earlier experimental series produced no visible damage, even when applied for 40 seconds.

Table II shows that the results of our experiments substantiated our assumption.

Table II

Nr.	Contrast solution	Injection time	Application time prolonged by ischemia	Total application time	Vascular lesion
1	Umbradil 35 p. c. 12 ml.	40 sec.	30 sec.	70 sec.*	—
2	Umbradil forte 50 p. c. 5 ml. ..	1 sec.	9 sec.	10 sec.	—
3	Umbradil forte 50 p. c. 6 ml. ..	2 sec.	23 sec.	25 sec.	+
4	Umbradil forte 50 p. c. 4 ml. ..	1 sec.	36 sec.	37 sec.	+

* It is remarkable that no injury occurred in this case in spite of such a long application time as 70 seconds. The negative result is, however, not incompatible with the positive result obtained on repeated injection in the previous series (table I), because the total application time in these experiments was 90 to 120 seconds.

3. *Experiments with the combined effect of a contrast medium and another chemo-toxic or physico-chemical agent.*

The purpose of the present experimental series was to find out whether the combination of 2 injurious substances capable of affecting the cerebral vessels could produce an injury when administered in concentrations known to be non-injurious when applied by themselves. Such a summation effect can presumably be tested by injecting a mixture of the two substances or by injecting them in rapid succession.

In an earlier study we produced evidence showing that the injurious effect of contrast media of the diodrast group on the cerebral vessels is due to a chemo-toxic activity and that the injury cannot be explained solely by the osmotic action of the concentrated solutions (Broman and Olle Olsson, 1949). In some experiments we mixed 35 per cent umbradil with a varying amount of NaCl to determine whether the cerebral vessels

could be damaged by the mixture, even if the osmotic pressure was considerably lower than that which was shown earlier to be injurious (Broman and Lindberg-Broman, 1945; Broman and Olle Olsson, 1949). If this should be the case, it would argue for the possibility of a summation effect of osmotic and chemo-toxic factors. The result, however, showed that the addition of 1 per cent NaCl produced no injury, in spite of an application time of 30 seconds. The addition of 2 per cent NaCl damaged the vessels, but with this concentration the osmotic pressure was near that proved injurious in the above-mentioned earlier investigations. We were thus unable to demonstrate a summation effect in this case.

In another experimental series the injection of 35 per cent umbradil solution was combined with another chemo-toxic substance, such as formalin, which is known to be a pronounced cellular poison. The injection of this substance is admittedly attended by the disadvantage of having such a serious effect on the general condition of the animals that they easily die. On the other hand, and remarkably enough, it was shown to have the advantage that when the doses chosen were so small as not to be fatal, the cerebral vessels were not damaged. In these summation tests we adopted the following technique. A cannula attached to a rubber tube was filled with formalin up to the syringe, which contained 35 per cent umbradil. Hence, on injection the small quantity (approx. 1.6 ml) of 10 per cent formalin solution first injected into the artery was followed immediately by the umbradil solution. The animals generally survived the injection easily. Table III (rabbits) shows the result of this examination series.

Table III

Nr.	Injection of	Convulsions	Impaired permeability	Stasis
1	10 ml. 5 p. c. formalin/3 sec.	+	—	—
2	16 ml. 10 p. c. formalin/6 sec.	— (death)	— (post-mort. test)	—
3	1.6 ml. 10 p. c. formalin followed by 20 ml. physiologic saline/10 sec.	(+)	—	—
4	1.6 ml. 10 p. c. formalin followed by 5 ml. physiologic saline/5 sec.	—	—	—
5	1.6 ml. 10 p. c. formalin followed by 50 ml. 35 p. c. umbradil 30/sec.	(+)	+++	+
6	1.6 ml. 10 p. c. formalin followed by 50 ml. 35 p. c. umbradil/30 sec.	++	+++	+

Table III shows that 35 per cent umbradil solution which — when applied by itself for so short a time as 30 seconds — will have no injurious effect on the cerebral vessels, will be followed by a pronounced disorder

in the permeability of the cerebral vessels if the injection (30 secs.) is preceded immediately by an injection of an otherwise non-injurious dose of formalin. The positive result suggests that a latent vascular injury lesion not attended by a disturbance of the permeability may be aggravated and become manifest by the effect of such a slightly injurious contrast medium as 35 per cent umbradil.

In another experimental series (table IV) we combined the injection of 35 per cent umbradil with a chemo-toxic substance, a bile salt, natrium taurocholate (the permeability disturbing effect of bile salts in the cerebral vessels was demonstrated earlier by BROMAN and LINDBERG-BROMAN 1945). After preliminary tests of its possibly injurious effect, it was observed that a 1 per cent solution, even when applied for 45 seconds, caused no disturbance of the permeability. On the other hand, a 2 per cent solution was rapidly followed by a slight impairment. The injection of a 1 per cent solution of sodium taurocholate in 35 per cent umbradil, applied for 30 seconds, produced a slight disturbance of the permeability, and in one experiment with an application time of 35 seconds a somewhat graver disturbance of the permeability was observed.

Table IV

Nr.	Injection of	Convulsions	Impaired permeability	Stasis
1	50 ml. 1 p. c. natrium-taurocholate/30 sec.	—	—	—
2	80 » 1 » » » »	—	—	—
3	80 » 1 » » » /40 sec.	—	—	—
4	80 » 1 » » » /45 sec.	—	—	—
5	50 » 2 » » » /30 sec.	—	+	—
6	50 » 2 » » » »	—	+	—
7	50 » 5 » » » »		+	
8	80 » 1 » » » » dissolved in 35 p. c. umbradil	—	+	—
9	80 » 1 » natrium-taurocholate /35 sec. dissolved in 35 p. c. umbradil	+	++	—

Table IV shows that the minimum application time necessary for either one of 2 injurious agents to damage the cerebral vessels can be considerably reduced if both agents are applied simultaneously.

Discussion

The risk of damage to the cerebral vessels incidental to cerebral angiography is presumedly dependent mainly on the type and quantity of the contrast medium used and on the application time of the individual injections (cf. earlier studies: BROMAN and OLLE OLSSON, 1948—49). But the

occasional co-existence of other factors might possibly favour the occurrence of an injury.

Particularly the effects of repeated injections were examined as possible aggravating factors. It was found that if the injections were given in rapid succession, *i. e.* at intervals of a few minutes, the permeability of the vessels was disturbed even though the concentration and the application time of the individual injections were within otherwise critical limits. This warrants the conclusion that, at least in certain cerebral angiographic examinations requiring repeated exposures and injections, the injections should not be given at shorter intervals than 15 minutes.

We may also assume that the nature of a cerebral disease motivating cerebral angiography may be partly responsible for the occurrence of damage to the cerebral vessels incidental to angiography. The part played by primary disease process may be manifold. In vascular diseases, for example, the focal circulation may be retarded, as may also be the case perifocally around expansive processes.

In the present study we showed experimentally that the effect of a retarded circulation in the brain produces symptoms comparable to those seen on prolonged application time of the medium. Even the brief injection of a relatively small amount of contrast medium (umbradil forte), which by itself would normally not have any untoward effect on the vessels, damaged them when the circulation was retarded. Hence, there is reason to assume that in spite of all precautionary measures the cerebral vessels may be damaged occasionally — at least regionally — in association with cerebral angiography. Clinical experience points in the same direction (Olle Olsson, 1949).

There is feasibly also another possibility for a cerebral disease to favour damage to the cerebral vessels incidental to angiography. The disease process may cause a latent or manifest but slight vascular injury, which might be aggravated considerably by the effect of the contrast medium. In order to form a conception of this possibility, we endeavoured to find out whether the cerebral vessels can be damaged by the summation effect of 2 substances with different chemo-toxic effects (one of which was the contrast medium umbradil 35 per cent which had been found to be least toxic in an earlier investigation), which were administered in quantities not injurious if each substance was administered by itself. As the resultant summation effect was positive, there is reason to assume that slight cerebral changes such as threatening edema of the brain and toxic encephalopathies around infectious or necrotic tissues may be aggravated considerably by the contrast media injected in association with angiography.

SUMMARY

The purpose of the study was to find out whether certain clinical conditions or technical factors are liable to increase the risk of damage to the cerebral vessels in cerebral angiography with the contrast media of the diodrast type. The following results were obtained.

Repeated injection of a contrast medium into the carotid artery involves a risk of a summation-effect if the interval between the individual injections is short. Even slightly toxic contrast media are injurious if injected in this manner.

Retardation of the circulation in the brain will prolong the application time and lead to an injury, even though the contrast medium is injected fairly quickly.

Latent vascular injury in the brain is liable to be aggravated and become manifest by the injection of a contrast medium of the diodrast type in cerebral angiography. This was demonstrated experimentally by injecting another chemo-toxic substance in an otherwise non-injurious quantity immediately before, or simultaneously with, the injection of the contrast solution. Certain cerebral disease processes may presumably have a similar effect.

ZUSAMMENFASSUNG

Die hier vorliegende Untersuchung bezweckt festzustellen, inwieweit anzunehmen ist, dass gewisse klinische Krankheitszustände oder technische Verfahren bei zerebraler Angiographie mit Kontrastmittel vom Typus des Diodrast die Gefahr einer Schädigung der Gehirngefässe vermehren können. Man kam zu folgenden Ergebnissen:

Bei wiederholter Einspritzung von Kontrastmittel in die Arteria carotis liegt die Gefahr einer Summationswirkung vor, wenn die einzelnen Injektionen zu dicht aufeinander folgen. Hierbei kann selbst bei Verwendung verhältnismässig wenig toxischer Kontrastmittel eine Schädigung auftreten.

Wenn im Gehirn oder einer Partie desselben die Blutströmung verlangsamt ist, so bedeutet dies eine Verlängerung der Applikationsdauer, so dass eine Schädigung entstehen kann, selbst wenn das Kontrastmittel verhältnismässig rasch eingespritzt wird.

Wenn im Gehirn eine latente Gefässschädigung vorliegt, so besteht die Gefahr des Manifestwerdens derselben, wenn man bei einer zerebralen Angiographie ein Kontrastmittel vom Typus des Diodrast einspritzt. Dies lies sich experimentell nachweisen durch Zufuhr einer anderen chemisch-toxischen Substanz in an und für sich unschädlicher Menge unmittelbar vor oder gleichzeitig mit der Einspritzung von der Kontrastlösung. Es ist anzunehmen, dass gewisse zerebrale Krankheitsvorgänge die gleiche Wirkung haben.

RÉSUMÉ

La présente étude a pour but de préciser dans quelle mesure on peut admettre que certains états pathologiques, ou encore certains procédés techniques, augmentent le risque de voir survenir des lesions vasculaires au niveau du cerveau lors des examens angiographiques de cet organe au moyen de substances de contraste du type du Diodraste. Voici les résultats obtenus:

Le danger d'un effet de sommation existe quand on répète à courts intervalles les injections de la substance opaque dans la carotide. Alors, des dommages peuvent être causés même avec des produits relativement peu toxiques.

Quand la circulation sanguine est ralentie dans le cerveau, ou dans certaines de ses parties il en résulte une prolongation de la durée d'application qui peut aller jusqu'à provoquer des lésions, même avec une injection relativement rapide.

Une lésion vasculaire latente du cerveau risque de devenir manifeste par l'injection d'une substance de contraste du type du Diodraste, à l'occasion d'un examen angiographique. Ce fait a pu être démontré expérimentalement en administrant, juste avant l'injection de la substance de contraste, un autre corps toxique, de nature chimique, mais à une dose qui par elle-même serait inoffensive. On peut admettre que certains processus pathologiques au niveau du cerveau entraînent des effets semblables.

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